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## MEDICAL SCIENCES

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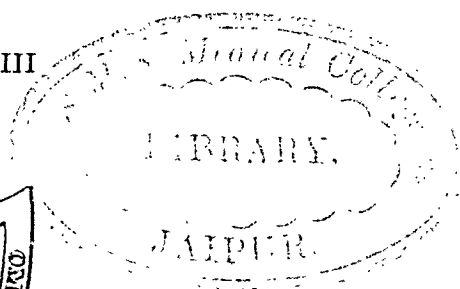
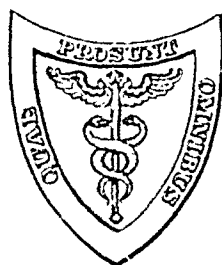
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ASSISTANT EDITOR

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ORIGINAL ARTICLES.

OBSERVATIONS ON THE APPARENT ADAPTABILITY OF THE  
BODY TO INFECTIONS, UNUSUAL HARDSHIPS, CHANG-  
ING ENVIRONMENT AND PROLONGED STRENUOUS  
EXERTION.\*

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of the Chest, Jefferson Hospital.)

THE possibility that certain untoward effects may occur following prolonged exercise has been considered seriously in recent years. The interest is due largely to the increasing number of endurance contests (swimming and running) and the fact that a number of prominent athletes have succumbed to heart disease and pulmonary tuberculosis. Critical data, however, to prove that physical effort is injurious or shortens the expectancy of life of the normal individual are not easily obtained. Obviously it is as difficult to estimate the potential endurance of an individual as it is impossible to predict the degree of resistance to infection. The problem is confused further because of the frail appearance of many athletes who perform with unusual ability over a long period of time. Malnutri-

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tion, upper respiratory infection and oral sepsis are not uncommon and yet so far as determined longevity compares favorably with nonathletic individuals of similar station in life. It has been suggested as an explanation for untoward effects, that a pathologic state existed before the onset of strenuous effort and that exercise exerted merely a precipitating influence. So far as we are aware this impression has not been finally proved or disproved.

Abraham,<sup>1</sup> MacKenzie<sup>2</sup> and Bainbridge<sup>3</sup> have reviewed the literature on the physiology and certain clinical aspects of muscular exercise. It appears that the majority of studies referred to have been made at the onset or immediately following exertion. Apparently there have been few opportunities to study the phenomena of recuperation or the results of early athletic training and competition. The tabulation of untoward effects has been acquired largely through questionnaires sponsored by universities and athletic associations. It will be several years perhaps before adequate data are obtained for final analysis.

In the past, the study of disease has depended to a considerable extent on the presentation of data for follow-up and evaluation in later years. One of the attempts to apply this plan of investigation to a study of the effects of marathon running was instituted at the Peter Bent Brigham Hospital in 1923.<sup>4, 5, 6</sup> In the first series of studies (1923), no cardiac hypertrophy, resulting from many years of prolonged vigorous effort, was noted and immediately following the race there was no evidence of dilatation (in a few instances the hearts were temporarily smaller than at the beginning of the race). In the second series of studies, concerned with an examination of the chemical constituents of the blood (1924), the sugar content was moderately low in two runners and markedly decreased in four. There was a close correlation between the physical condition of the athletes at the finish of the race and the level of the blood sugar. In the third series (1925) runners who had hypoglycemia or manifested hypoglycemic-like phenomena were placed on a high carbohydrate diet and administered dextrose in the form of candy during the race. The blood studies in all athletes showed normal sugar levels and improved physical condition in contrast with the low figures previously noted.

Nine runners of the group first observed in 1923 have been examined between races during the past six years. So far as determined no important changes have occurred other than increased lung markings and the usual evidence of advancing years comparable with those noted in most athletes accustomed to less strenuous forms of exercise.

The opportunity to study a large group of long-distance runners in daily competition occurred in March, April and May, 1928, during a transcontinental foot race from Los Angeles to New York City. Since the course of the race extended through Oklahoma, Arizona,

New Mexico, Missouri, Ohio, Illinois, Pennsylvania and New York, a wide variation in altitude, climate and road conditions was inevitable. It appeared, at the beginning of the race, that however efficiently the contest was managed, there would be unusual difficulties in providing suitable clothing, food and shelter and in preventing or treating injuries and infections. Apart from the interest in determining the immediate untoward effects of strenuous prolonged effort and the adaptability of the body to an unusual and rapidly changing environment, it seemed that the data acquired would be of value in follow-up studies in later years.

**The Plan of Study.** A detailed history of past infections and various experiences in athletic training and competition were obtained in 90 competitors before the start of the race. A physical examination, including a study of the urine, vital capacity and blood pressure was also made. One of us (J. C. B.) accompanied the runners during the entire race and recorded at frequent intervals changes in the physical signs and general appearance of the athletes. The causes for withdrawing from the race and the effects of weather, altitudes, road conditions, epidemic infections, types of food consumed, dietary habits, hours of sleep, the mental attitude of the runners and the ability to cope with various problems, particularly in the face of injury were noted.

**Observations before the Race.** In the race, 199 competitors were entered from almost every country in the world and 29 states in America. The oldest runner was sixty-four years of age and the youngest was seventeen years. In the entire group not over forty competitors appeared capable of withstanding strenuous athletic competition. Six runners were found to be suffering from acute respiratory infections, 9 had gastrointestinal symptoms. One runner had signs of active pleurisy, 4 had chronic bronchitis, 11 had moderate emphysema, one had a morning temperature of 102° and 18 had more or less serious contusions of the feet, legs or knees. Approximately 50 per cent of all competitors were underdeveloped physically and could scarcely be compared with long distance runners usually seen in universities or athletic clubs. It was found that only 6 runners, in preparation for the race, ran over 25 miles daily and comparatively few had competed in important long-distance races. There was an extremely wide difference of opinion as to the most effective style of running. The advisability of massage, treatment of injuries, and the most desirable foods, were questions about which there was no general agreement. The vital capacity estimations, according to accepted standards,<sup>7</sup> were found to be within normal limits except in 8 runners who showed an average increase of 15 per cent and 7 who had a decrease of 5 per cent. The blood-pressure readings were essentially normal but the heart rates were usually low (50 to 65). Systolic murmurs at the apex were noted in 12 runners. In the examination of the urine there

were 17 instances of albumin, three specimens showing hyaline casts and several white blood cells.

**Observations during the Race.** The first three weeks of the race were characterized by almost every violation of the accepted principles of diet and hygiene and disregard for physical injury, infection and human endurance. Numerous fads and fancies were evident in the selection of food and in the time and manner of eating. Raw, dry or thoroughly cooked foods were advocated by some; other competitors selected high-protein diets including large portions of meat, high carbohydrate or strictly vegetarian foods. Some runners were as strictly opposed to drinking water or eating between meals as others were in favor of consuming carbohydrate while running.

The general appearance of most runners after completion of the daily mileage was that of exhaustion with cold perspiration, dyspnea, drawn facial expression, hunger, thirst and a desire to sleep. Tonsillitis, diarrhea, shin splints,\* injuries to the feet, pains in the abdomen, blisters due to sun and wind, albumin, red and white blood cells in the urine, transient extra systoles and increased heart rate were among some of the manifestations noted. The extent and rapidity of recuperation depended largely on the amount of sleep, the quantity and quality of food, the disappearance of infection and physical injuries. It was noteworthy that few participants regarded infections or injuries with great concern, whereas officials advised runners repeatedly to seek medical care and retire from the race. It appeared that the chief cause for withdrawal however, was the occurrence of pain and stiffness in the limbs which prolonged the running time and thus rendered remote the chances to finish within the first third.

As the race progressed complications, in addition to those previously noted, were as follows: Boils (one rectal abscess), diarrhea, tympanites, sudden elevation of temperature while running, nausea, acute upper respiratory infections with fever of 100° to 101°, loss of toe nails, blisters of the feet and injuries from passing automobiles. The physical discomfort was aggravated often by high winds; sudden changes in altitude and temperature, dusty, alkali or muddy roads. It was impossible after the first two weeks to provide the runners with desired types of food. One runner continued to eat raw food, several maintained strict vegetarian diets, but the majority

\* Shin splints result from myositis and accompanying periostitis, the extensor muscles of the lower lateral aspect of the legs being chiefly involved. The condition is characterized by redness, swelling, pain and tenderness. The symptoms usually subside in eight or nine days but not infrequently stiffness, "knotting" and shortening of the muscles occur. Fibrous tissue is often palpable. Ideal treatment consists of rest and application of heat; massage is contraindicated. Obviously judicious treatment could not be carried out if the runners were actively engaged in the contest. It was interesting to note that "shin splints" did not occur in the English runners, who ran in a more or less flat-footed manner, lifting the feet not more than 3 or 4 inches from the ground.

consumed without restriction. A change which was almost general was the consumption, while running, of oranges, lemons, dates, figs, chocolate or dextrose in the form of lozenges. Several competitors used tobacco and in addition to eating between meals drank coffee with or without generous helpings of sucrose at the end of the daily lap. Although an average of two or three competitors retired weekly throughout the race, with few exceptions the causes were financial, loss of interest, or injuries to the feet. So far as determined there were only 7 instances of exhaustion and these appeared to result from the lack of training and physical incapacity evident before the start of the race. The race lasted for eighty-four days, the daily average mileage was 44.2, the total distance was 3484 miles, the greatest daily distance covered was 72 miles. When the race was ended in New York City 14 runners (57 completed the race) showed evidence of fatigue, lameness and loss of weight. The remaining athletes appeared in excellent health and ran the last 25 miles in less than two hours and fifty minutes. It was striking to note that 9 runners were as free from dyspnea, fatigue and perspiration as would be expected from athletes who had completed a series of moderate calisthenic exercises.

**Observations after the Race.** Three days after the finish of the race 25 runners, who had covered the entire distance, and two participants who walked or ran approximately 2000 miles, were brought to the Chest Department of the Jefferson Hospital for a general physical examination. The observations, made possible through the coöperation of members of the staff of the Jefferson Medical College and Hospital included microscopic and chemical studies of the blood and urine, roentgenographic, electrocardiographic, ophthalmoscopic, orthopedic and laryngeal examinations. The data noted in the general physical examination are as follows: pulsation of veins of the neck, 1; emphysematous type of chest, 5; abdominal type breathing (predominating), 7; delayed respiratory expansion on one side of the chest, 2; distant breath sounds throughout, 9; pleural friction rub at right base (history of pleurisy nine years previous), 1; pleural friction rub at left base (noted in the beginning of the race), 1; râles at the apex with impaired percussion note (history of infection suggesting pulmonary tuberculosis twelve years ago), 1; forceful apex beat, 2; systolic murmur at apex, 9; extra systoles, 1. The pulse rates varied between 50 and 80; blood pressures varied between 105 and 150 systolic; 55 and 85 diastolic.

The ophthalmologic examination showed the fundus redder than normal in 12 runners, the disk margin hazy in 4, the vessels slightly fuller than normal in 5 runners.

The orthopedic examination showed 5 instances of palpable edema along the anterior tibial margins; considerable callous on the plantar surface of the feet in 6 runners; tenderness and swelling of the ten-

don of Achilles in two and tenderness of the soft portions of the anterior tendons of the feet in three runners. Ill-fitting shoes were used by 18 runners. No bunions were noted.

The surgical examination showed the presence of varicosities in four runners (one had been present for twenty-one years) and one hernia which was noted before the race.

The laryngeal examination showed varying degrees of caseous, hypertrophic and cryptic tonsillitis in 17 runners. Inflammation of the nasal mucosa with discharge was noted in 13 instances.

In the examination of the urine, a series of specific gravity tests showed a variation between 1010 and 1018; no casts or red blood cells were found. The specimens were free from albumin, acetone and according to the Benedict qualitative method, no sugar was noted.

In the examination of the blood, the red blood cells varied between 5,000,000 and 5,800,000; the white blood cells between 4700 and 6000; the hemoglobin (Dare—candle) varied between 90 and 98 per cent. The blood smears were essentially normal.

The highest estimation for nonprotein N of the blood was 41.5 and the lowest 35.5 mg. (per 100 cc. of blood); the highest blood sugar was 0.101 and the lowest was 0.092 mg. (per 100 cc. of blood).

In the roentgenographic studies made to determine the effect of prolonged effort on the heart, lungs, bones and bloodvessels, the lungs in general were found to be normal. The bones, except for osteoarthritic changes, were essentially normal except in the older runners. The bloodvessels in the older runners showed no evidence of sclerosis. In 13 runners, the hearts appeared to be definitely smaller than normal; in 5 runners, the hearts were within normal limits; and in five instances, the hearts, according to the table of Bardeen, showed an increase in size. According to the so-called cardiothoracic ratio, only one heart was increased in size and this occurred in the oldest runner. The roentgenographic data as a whole suggest that the effects of exercise are inconsequential since all of the changes noted may be found in individuals of similar ages who have no symptomatic complaints.

In the electrocardiographic examinations there was a tendency to a rather high take-off of the "T" and a large excursion of the "P" waves in 4 runners and extra systoles in two instances. The tracings were not entirely satisfactory in 7 runners.

It was interesting to note that runners who had shown lameness and fatigue at the finish of the race were considerably improved and that 5 runners had gained 3 pounds in weight.

Since the completion of these examinations correspondence has been carried on with the group observed in Philadelphia and 34 additional athletes, in order to determine the course of events following the return to normal life. Some of the answers to the questionnaires were as follows: "I am in good health, in fact I never felt

better in my life." "After returning to my home I climbed a mountain 11,824 feet high and experienced no difficulty." "My legs which were sore are all right now and I am able to run." "Feel fine and fit." "My weight increased from 140 to 166 pounds and I became tired, then I started to train and now feel fine and will enter races in the future." "My doctor says I am just as sound as ever." "I am running every morning at least 40 miles and the Sunday before Christmas I ran 72 miles and finished in excellent shape." "There is not one thing wrong with me."

**Comment.** It is agreed that certain individuals accustomed to leading sedentary lives and others affected with degenerative changes are in danger of catastrophe during the performance of strenuous exercise. The question, however, as to whether restriction of physical effort in the comparatively normal active individual may be unnecessary and perhaps actually harmful, is unsettled. The unique performance of 52 adult individuals running an average of 42 miles for eighty-four consecutive days in an environment comparable only with frontier life of seventy-five years ago, suggests that factors other than work should be considered in appraising the capacity of endurance of the human body. A solution of the causes for fatalities in athletes may be found in differentiating between nervous influences and metabolic disturbances under brief strenuous competition and the effects of prolonged daily running. Obviously the data presented in the report must be considered critically because some of the observations were made under circumstances not conducive to thorough study. The investigation is reported primarily to suggest that the human body during exercise may acquire extraordinary capacity for work and resistance to infection.

**Conclusions.** 1. A study of 199 participants in a transcontinental foot race was made to determine the qualifications for successful competition and the effects of prolonged daily exertion.

2. A marked difference was noted in the age, nationality, physical development, experience in running and habits of food consumption.

3. The race was characterized by almost every violation of the accepted principles of diet, hygiene and disregard for injuries, infection and human endurance.

4. The chief causes for withdrawal were so-called "shin splints," financial difficulties and lack of interest in the contest. So far as determined there were only seven instances of exhaustion and these appeared to result from the lack of training and physical capacity evident before the start of the race.

5. It appeared that a high caloric intake, derived from all foods, was more important than any fixed dietetic régime. The most successful runners consumed readily available carbohydrate between meals, followed an unrestricted high caloric diet at meal time and ingested meat at the evening meal.

6. The details of a complete physical examination made three days

after the finish of the race are tabulated. Abstracts from correspondence with runners eight months after the return to normal life are recorded.

7. The data suggest that the comparatively normal human body, provided with adequate food and rest, may acquire during prolonged exercise unusual capacity for work apparently without serious untoward effect.

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## BRONCHOSCOPIC FINDINGS IN LOBAR PNEUMONIA.\*

### A PRELIMINARY NOTE.

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IN previous papers,<sup>1,2,3</sup> experimental and clinical data were given upon which was based the opinion that pneumococcic pneumonia should be considered as a pneumococcic atelectasis.

Experimental pneumonia was produced in dogs by intrabronchial insufflation of eighteen-hour-old cultures in broth of pneumococcus Type I, concentrated ten times by centrifugation.

One or two cc. of the culture was insufflated in a chosen bronchus by means of a bronchoscope after intraperitoneal anesthesia with

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isoamyl ethyl barbituric acid (amytal), 10 per cent, 55 mg. per kilogram. Almost constantly a lobar pneumonia was obtained, confined to the insufflated lung, and occasionally in the noninsufflated lung. The roentgenograms were invariably those of atelectasis due to bronchial obstruction, namely, opacity of the affected lobe, elevation of the corresponding diaphragm and displacement of the heart and mediastinum to the affected side. Bronchoscopic examination of those animals showed that the bronchus of the affected lung or lobe did not breathe. Bronchoscopic aspiration yielded variable amounts of brownish viscid fluid from the corresponding lung. After aspiration the lung often became somewhat aërated, but we were unable to save the animals, the pneumonic process continuing after variable period of relief.

The roentgenographic similarities between atelectasis and pneumonia in experimental cases drew my attention to the corresponding similarities in man. These similarities are more than mere coincidences, and a thorough study of them can lead to an explanation of a number of features in pneumonia as yet unexplained. These features are: (1) The lobar distribution of the disease; (2) the short prodromic period in which symptoms of a slight bronchial catarrh may be present; (3) the sudden onset; (4) the diminished or absent breath sounds at the onset with tympanitic dullness; (5) the wedge-shaped roentgenographic shadow at the very onset of the disease; (6) the abortive forms which after twenty-four to forty-eight hours terminate by crisis or rapid lysis, often with abundant expectoration; (7) the predominance of pneumonia in the lower lobes and especially the right; (8) and the peculiar regularity with which crisis or lysis usually occur between the fifth and thirteenth day.

Still greater are the similarities between postoperative atelectasis and postoperative pneumonia, the most striking of which are: (1) The onset of both within twenty-four to forty-eight hours after operation, especially upon the upper abdomen; (2) the presence of pneumococcus Group IV in the sputum in both; (3) the frequent impossibility of a clear-cut differential diagnosis between them, from clinical, Roentgen or laboratory data; (4) the similarities in the pathologic findings.

Displacement of the trachea and mediastinum to the affected side with elevation of the diaphragm on this side has been reported in postoperative as well as medical lobar pneumonia in the human. The fact that this displacement is less marked in pneumonia than in simple atelectasis would be due to the pneumococcic cellulitis and alveolar exudate complicating the pneumococcic atelectasis. Moreover, never does displacement of the mediastinum toward the sound side occur in uncomplicated pneumonia, although there is a common belief that the pneumonic lung is larger than the healthy one. As these two facts seem contradictory, and as in experimental cases of pneumonia in dogs the affected lung is found to be smaller, if the



precaution is taken to clamp the trachea before opening the chest, I tried to determine the true size of the pneumonic lung in the human compared to the healthy lung. For this purpose in Case III, the trachea was clamped before opening the chest, in order to avoid collapse of the healthy lung, and it was found that the affected lung was *slightly smaller than the healthy one*. Last, it is of more than passing interest to note that in 95 per cent of cases of lobar pneumonia the organism concerned is the pneumococcus, which is precisely *the microbe causing an exudate rich in fibrin, most tenacious and highly viscid*. The *Bacillus friedländer* which also gives quite a viscid exudate, often produces the lobar type of pneumonia.

It therefore seems reasonable to consider that in the human being in the course of a pneumococcic bronchitis this viscid exudate could occlude a lobar bronchus and cause a lobar pneumonia, in much the same way that the occlusion of a bronchus causes lobar atelectasis. If this conception be right, lobar pneumonia would start as a pneumococcic atelectasis, more or less toxic, according to the virulence of the causative pneumococcus.

A solution of this problem was only possible by bronchoscopic examination of human cases of lobar pneumonia, in order to determine whether the bronchus of the affected lobe was occluded and what the result of aspiration of such a bronchus would be. The possible risks of bronchoscopy for pneumonia patients having been discussed with Drs. L. Conner, A. Lambert and J. Kernan, the procedure was carried out in order to submit our theory to a practical test. Nine cases of lobar pneumonia were bronchoscoped by Dr. Kernan and myself, 3 at New York Hospital, first division, and 6 at Bellevue Hospital, fourth division, without any change in the usual routine pneumonia treatment. (No serum was given to these patients except in Case I.)

**Technique.** The bronchoscopic technique was the following: One hour before the bronchoscopy,  $1\frac{1}{2}$  gr. of luminal was given to the patient. Local anesthesia of the throat and larynx was performed with 5 per cent cocain, and subsequent anesthesia of the trachea and the bronchi with the same solution atomized through the bronchoscope. For the aspiration we used the Gabriel Tucker vertebrated aspirating tube with a spring tip. As the aspiration of the very viscid fluid is very difficult, I thought that perhaps it would be easier to dislodge the exudate by introducing the tip of the tube as far as possible into the bronchus and insufflating air into it, using the aspirating bronchoscope at the same time. The result corroborated this hypothesis, and it has been possible this way to obtain more exudate than with simple suction. Our patients withstood this procedure very well; none of them showed the slightest shock or discomfort after it. On the contrary, as a rule, even in the patients who did not expectorate before, an abundant expectoration fol-

lowed the bronchoscopy the same as in cases of atelectasis, and a more or less marked relief was noticed. I give here a condensed résumé of these cases.

**Case Reports.** CASE I.—(N. Y. Hosp. First Div., December 29, 1928.) G. S., aged nineteen years, onset *thirteen hours before admission*. Temperature, 103°; pulse, 140; respiration, 26; Roentgen ray showed increased density of right lower lobe posteriorly with trachea slightly deviated to the right; right diaphragm elevated. White blood cells, 13,000; polymorphonuclears, 90 per cent. *Bronchoscopy five hours after admission, with cocaine anesthesia. Trachea displaced to the right. There was thick rusty purulent sputum coming from the posterior inner branch of the lower bronchus which seemed occluded and was aspirated until its mouth was clear; air was then insufflated to create an airway.* There was very little reaction to the bronchoscopy. Physical and Roentgen ray signs a few days later pointed to a marked involvement of right lower lobe; the general condition was good. Three days later (sixth day in Hospital) there was extension to right upper and middle lobes with rising temperature and pulse, and patient critically ill; on the following day Felton's serum was started and 165 cc. was given over a period of thirty-six hours. On the tenth day of the Hospital stay temperature was normal.

CASE II.—(Bellevue Hosp., Fourth Div., February 8, 1928.) F. N., aged forty-seven years. Admitted to hospital *twenty-four hours after onset of acute illness*. Temperature, 101.2°; pulse, 110; respiration, 24; white blood cells, 15,000; polymorphonuclears, 93 per cent. There was diminished breathing and dullness over left lower lobe; heart moderately drawn to the left. *Bronchoscopy twelve hours after admission showed thick mucopus occluding the anterior division of left lower bronchus. Following bronchoscopy patient started to cough up thick serosanguinous fluid with few viscid pellets of mucus, and seemed relieved by this procedure.* Four ounces were coughed up in ten hours. Temperature was normal three days after bronchoscopy, but signs developed over other areas; there were two or three recurrences of fever. Recovery sixteen days of disease.

CASE III.—(Bellevue Hosp., Fourth Div., February 10, 1928.) H. H., aged sixty-one years, acute onset was *apparently on the afternoon of admission*, temperature, 106°; pulse, 40; respiration, 28; white blood cells, 12,000; polymorphonuclears, 88 per cent; blood culture positive for Type I. *Bronchoscopy forty-four hours after admission (with temperature 100.5°; pulse, 90; respiration, 22) showed the posterior branch of the right lower lobe bronchus exuding a small amount of rusty sputum especially on coughing; air was insufflated into it to establish an airway; this seemed to release a considerable amount of rusty mucopus.* Twelve hours later patient was quiet comfortable with no pain on chest, and temperature fell to normal in twenty-four hours later; but the next day signs of a right upper lobe involvement appeared; pulse and temperature were rising although general condition was good. Fifty-two hours later marked pulmonary edema developed and patient expired on sixth day after that disease.

*Autopsy.* Chest opened after trachea was clamped. Lobar pneumonia of upper and lower right lobes; affected lobes were smaller than the healthy ones.

CASE IV.—(N. Y. Hosp. First Div., December 18, 1928.) T. C., aged twenty-four years, had had productive cough and coryza for two weeks; acute onset twenty-four hours before admission, with cough and blood-

tinged sputum, temperature,  $104^{\circ}$ ; pulse, 130; respiration, 46; white blood cells, 11,800; polymorphonuclears, 88 per cent; sputum, Type IV; blood culture, negative. Roentgen ray showed increased density of lower half of right chest, trachea deviated to the right, the right diaphragm at fourth interspace. *Bronchoscopy fourteen hours later right upper and middle bronchi clear. As the tube came down, sputum was coughed from the first dorsal branch of inferior lobe bronchus which was thoroughly aspirated. On coughing more mucopurulent material came from the lower bronchus and its branches, total sputum 20 cc.* Following bronchoscopy breath sounds at fourth interspace, right, became loud and bronchial; productive cough, but general condition good. Roentgen ray one hour after bronchoscopy showed decrease in density from seventh rib down; right diaphragm at tenth interspace; trachea still deviated to the right. Roentgen ray twenty-four hours later showed the right lower lobe clearing, but right upper and middle lobes were involved. Blood culture two days later was positive for Type IV; patient developed cyanosis and edema on the sixth day after admission. Temperature had declined slowly to  $102^{\circ}$ , since bronchoscopy, but pulse stayed high, reaching 130 before death.

CASE V.—(N. Y. Hosp., First Div., December 29, 1928.) E. F., aged twenty-three years, had had a productive cough for two weeks; acute onset was forty-eight hours before admission. Temperature,  $103.6^{\circ}$ ; pulse, 94; respiration, 30; white blood cells, 23,000; polymorphonuclears, 97 per cent; sputum, Type III; Roentgen-ray showed increased density of left lower lobe; left diaphragm slightly higher than the right; trachea slightly deviated to the left. *Bronchoscopy two hours after admission showed right posterior branch of the left lower bronchus occluded with a thick tenacious rusty exudate. Less than a teaspoonful of this material was aspirated. Other bronchi appeared normal.* There was no reaction from the bronchoscopy. Roentgen ray taken after the procedure showed no change. Crisis started thirty-six hours after bronchoscopy, temperature reaching normal in twelve hours and the patient clinically well. Physical signs persisted eight days more, and patient was discharged on sixteenth day after onset of illness.

CASE VI.—(Bellevue Hosp. Fourth Div., December 29, 1928.) J. N., aged thirty-two years, admitted to hospital with four days history of acute illness. Temperature,  $103^{\circ}$ ; pulse, 90; respiration, 24; white blood cells, 27,000; polymorphonuclears, 88 per cent; signs of right lower lobe dullness; heart displaced to the right and temperature  $104^{\circ}$ , were present on the day after admission. *Bronchoscopy sixty hours after admission showed that the right main bronchus normal; thin secretion coming from the first posterior branch. The mouth of the middle lobe bronchus was filled with thick rusty sputum and did not breathe with respiration; after exudate was removed it seemed that air was going in and out. Inferior lobe bronchus seemed clearer.* The temperature was normal sixty hours after bronchoscopy.

CASE VII.—(Bellevue Hosp., Fourth Div., February 7, 1928.) R. M., aged thirty-eight years, admitted with history of five days, there were dullness and friction rub over the right lower lobe. Temperature,  $98.6^{\circ}$ ; pulse, 110; respiration, 22; twenty-four hours later temperature was  $102.8^{\circ}$ ; pulse, 98; respiration, 28; white blood cells, 16,000; polymorphonuclears, 75 per cent; two days later temperature was  $101^{\circ}$ ; pulse, 98; respiration, 26; with signs of a more developed pneumonic process from sixth rib down; heart displaced 1 inch to the right. Diagnosis early right lower-lobe pneumonia. *Bronchoscopy was done twenty-four hours after onset; the mouth of the first dorsal branch of right inferior lobe of bronchus was red and obstructed; a curved-tip tube introduced and air was insufflated with a bulb, causing the*

appearance of light colored mucopus, a small amount of which was aspirated, temperature was normal forty-four hours after bronchoscopy.

CASE VIII.—(Bellevue Hosp., Fourth Div., February 13, 1928.) D. R., aged thirty-nine years, admitted in coma, after an alcoholic bout. Temperature,  $101^{\circ}$ ; pulse, 70; respiration, 24. On day after admission: Temperature,  $104^{\circ}$ ; pulse, 100; respiration, 28; white blood cells, 14,000; polymorphonuclears, 65 per cent. There was diminished breathing at right base with heart displaced to the right. Fluoroscopy showed haziness of right lower lobe, heart displaced to the right. Diagnosis early, right lower lobe pneumonia. *Bronchoscopy was done twenty-four hours after onset; the mouth of the first dorsal branch of right inferior lobe of the bronchus was red and obstructed, a curved tip tube introduced and air was insufflated with a bulb, causing the appearance of light-colored mucopus, a small amount of which was aspirated, temperature was normal forty-four hours after bronchoscopy.*

CASE IX.—(Bellevue Hosp., Fourth Div., February 11, 1928.) W. D., aged fifty-two years, admitted with an indefinite history with temperature  $101^{\circ}$ ; pulse, 80; respiration, 20; there were signs of middle right-lobe involvement, the man coughing up tenacious rusty sputum. On the third day of the disease, temperature,  $104^{\circ}$ ; pulse, 105; respiration, 28; white blood cells, 12,400; polymorphonuclears, 86 per cent; with marked right middle-lobe signs. *Bronchoscopy forty-eight hours after admission showed right middle-lobe bronchus occluded with tenacious mucopus and not breathing; 1 cc. of mucopus aspirated; from upper right bronchus viscid mucus flowed.* The temperature declined to  $100^{\circ}$  within ten hours after bronchoscopy, but the following day right lower-lobe signs were present, fever rose to  $104^{\circ}$ , and continued high with moderate remissions. On the tenth day of the disease the temperature rose to  $107^{\circ}$  and patient expired.

**Comment.** Bronchoscopic examination in the above cases has shown that in every case the bronchus corresponding to the consolidated area was occluded, and circulation of air was shut off. This tends to support the hypothesis that lobar atelectasis and lobar pneumonia are due to the same mechanism, namely, the occlusion of a bronchus.

TABLE I.—ANALYSIS OF BRONCHOSCOPED PNEUMONIA CASES.

No.	Patient	Age.	Admission, time after onset.	Bronchoscopy, time after onset.	Duration of disease.	Result.	Type of sputum.	Blood culture.
1	G S.	19	13 hours	28 hours	10 days	Recovered	1	Negative.
2	F N.	47	24 hours	36 hours	16 days	Recovered	1	
3	H. H.	61	?	49 hours	5 days	Death	1	Positive.
4	T. C.	24	24 hours	38 hours	8 days	Death	4	Positive.
5	E. F.	23	48 hours	48 hours	5 days	Recovered	3	Positive.
6	J. N.	32	4 days	8 days	10 days	Recovered	?	Negative.
7	R. M.	38	2 days	64 hours	11 days	Recovered	4	Negative.
8	D. R.	39	?	24 hours	3 days	Recovered	?	Negative.
9	W. D.	52	?	48 hours	9 days	Death	4	

Aspiration of the occluding exudate did not produce, in lobar pneumonia the same result as in simple atelectasis. Although the mortality of the bronchoscope cases was 33.3 per cent, whereas of the nonbronchoscope cases admitted in the same ward in Bellevue Hospital at the same short time it was 72 per cent (Table II), no conclusion should be drawn from this fact so far as a curative effect of this procedure is concerned. Not only because the number of the bronchoscope cases is so far very small, but also because the less toxic cases were taken for bronchoscopic investigation.

TABLE II.—ANALYSIS OF CONTROL PNEUMONIA CASES.

No.	Patient.	Age.	Admission, time after onset.	Duration of disease.	Result.	Type of sputum.	Blood culture.
1	S. C.	38	2 days	8 days	Death	1	Negative.
2	D. E.	35	2 days	4 days	Death	?	
3	G. N.	48	3 days	7 days	Death	1	
4	R. S.	22	3 days	9 days	Recovered	4	Negative.
5	J. B.	21	?	4 days	Recovered	4	Negative.
6	J. W.	49	4 days	12 days	Death	2	Negative.
7	W. B.	39	4 days	13 days	Recovered	1	Negative.
8	C. N.	23	4 days	6 days	Death	2	Negative.
9	C. B.	21	5 days	5 days	Recovered	1	Negative.
10	J. C.	53	7 days	12 days	Death	?	
11	J. M.	43	3 weeks	24 days	Death	2	
12	J. L.	63	?	4 days	Death	2	Positive.
13	M. S.	45	?	2 days	Death	1	Positive.
14	F. B.	66	?	5 days	Death	1 N	Negative.

Two facts only have been proven: the occlusion to the air of the bronchus corresponding to the consolidated area in human lobar pneumonia and the innocuousness of a correctly performed bronchoscopy on pneumonia cases.

**Conclusions.** 1. From the study of the above cases, it is clearly shown that the bronchoscopic examination of pneumonia patients, even when they are in poor general condition, is not a shock to the patient. On the contrary all of our patients felt more or less relieved in proportion to the amount of the exudate aspirated or spontaneously expectorated after bronchoscopy.

2. In every one of the bronchoscope cases the bronchus corresponding to the affected lung area, and only this one, was found occluded with viscid exudate and air circulation interrupted.

3. So far as the possibilities of the therapeutic influence of bronchoscopy in pneumonia is concerned, no opinion is expressed; this preliminary note has as its object only the presentation of the pathologic findings, which seem to support the experimental facts upon which the theory was based that lobar pneumonia starts as a pneumococcic atelectasis.

4. Displacement of the mediastinum and of the diaphragm to the affected side, especially at the early stages of the pneumonia is more frequent than is generally believed and can be found if carefully looked for.

5. The affected lobes in lobar pneumonia, contrary to the general belief, are smaller in size than the healthy ones.

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### THE SIZE OF THE CONSOLIDATED LUNG IN LOBAR PNEUMONIA.

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WHAT is the true size of the consolidated lung in lobar pneumonia? Are the consolidated lobes larger or smaller than the healthy ones?

In the textbooks of medicine and of pathology it is conceded without discussion that the affected lobes are increased in size. So far as we have been able to investigate there is no contrary opinion, nor any doubt expressed about this point.

Henri Barth,<sup>1</sup> in his article on pneumonia in the *Dictionnaire des Sciences Medicales* (1888), says that the "volume of the affected lung is always increased, and especially in the cases called massive pneumonia, where the affected lung is twice the size of the healthy lung." He adds, that Broussais was the first to notice that the lung in these cases presents on its surface longitudinal grooves due to the pressure exerted by the ribs upon the lung which is increased in size. Among modern authors, we shall quote F. Blake,<sup>2</sup> who states that "the lobes in the pneumonic process are larger than the unaffected lobes and fill the greater part of the pleural space." R. Murray Leslie<sup>3</sup> says "the consolidated lung becomes large and voluminous, its size being equal to that of full inspiration and shows longitudinal depressions or markings due to rib indentations."

Pathologists are more cautious on this subject. W. C. MacCallum<sup>4</sup> does not give any definite opinion on the subject. He describes the consolidated pneumonic lung as "dense, hard and heavy" (p. 317), and only in describing the aspect of the lung in gray hepatization (p. 519) does he say "that it is still more enlarged, dense and heavy." F. Delafield and T. M. Prudden<sup>5</sup> do not commit themselves on the subject. L. Aschoff,<sup>6</sup> however, states that "the affected lobes are immediately distinguished from the healthy ones because of their tense and voluminous aspect."

We have quoted only a few authors in order to show the unanimity of opinion on this subject. A careful analysis, however, of the physical and especially the roentgenographic signs of the disease are in contradiction to this general opinion; we shall briefly enumerate the more important among them. They are:

1. The constant elevation of the diaphragm on the affected side, even in cases involving the upper lobes. It is the general belief that this elevation is due to an inhibitory paralysis of the diaphragm. But, if this were the case, why does the heavy and voluminous lung not flatten the paralyzed diaphragm by its weight and size?

2. The tympany or skodaic resonance at the upper level of dullness. The explanation actually given is that this is due to the "compression of the lung adjacent to the consolidated area and the release of its elasticity." We confess that we do not understand how resonance will be increased by compression of the lung and the subsequent decrease in its air content.

3. The paravertebral area of relative resonance on the affected side in cases of unilateral extensive consolidation of the lower lobe described by F. T. Lord,<sup>7</sup> and known as the sonorous triangle of Lord. How could this resonant space exist on the affected side if the statement of Blake<sup>2</sup> be correct, that the affected lobes fill the greater part of the thoracic cavity?

4. The absence of the displacement of the heart and the trachea to the opposite side. If the pneumonic lung is enlarged, why does it not displace the mediastinum toward the healthy side? The healthy and perfectly elastic lung could not appreciably resist the pressure of the consolidated and supposedly enlarged pneumonic lung.

5. The often-reported displacement of the heart and the mediastinum toward the affected side, particularly in unilateral cases and more especially in children. Thoenes,<sup>8</sup> Wallgren<sup>9</sup> and St. Engel<sup>10</sup> reported a great number of cases of these "inexplicable displacements of the heart and mediastinum to the affected side." Furthermore, St. Engel pointed out that "the elevation of the diaphragm in lobar pneumonia is of common occurrence." Griffith,<sup>11</sup> in 1925, gave the history of a child in whom the diagnosis between atelectasis and pneumonia was impossible, and added that "lobar pneumonia



FIG. 1.—Dog B 41. Massive atelectasis of right lung, experimentally produced by obstruction of the right bronchus with an elastic balloon filled up with sodium iodid solution. Heart displaced to the right; right diaphragm elevated.

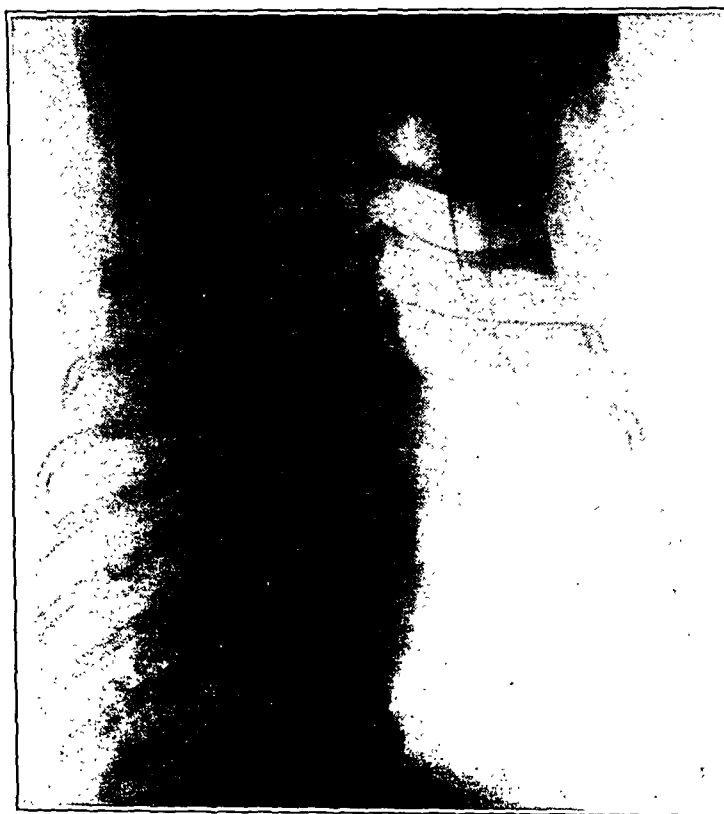


FIG. 2.—Dog B 40. Right pneumonia experimentally produced by insufflating in the right bronchus, pneumococcus culture, Type I. Ten cc. of twenty-hour old broth was centrifuged and the sediment suspended in one cc. of broth before insufflation. Heart displaced to the right; right diaphragm elevated as in Fig. 1.





FIG. 3.—Dog 251. Left massive atelectasis, experimentally produced by obstruction of left main bronchus.



FIG. 4.—Dog B 27. Left pneumonia. Same technique as in Fig. 2.

may at times be capable of producing similar if not perhaps as marked Roentgen ray appearances as seen in massive atelectasis." The same author,<sup>12</sup> in 1927, reported 40 cases of lobar pneumonia in children, 16 of which showed displacement of the heart to the affected side. Personally, going over old pneumonia plates in Bellevue and New York Hospitals, we discovered a considerable number showing displacement of the heart to the affected side, and this fact has been clinically verified by Dr. Alexander Lambert.<sup>13</sup>

The authors mentioned above explain the shift of the mediastinum by "compensatory hyperdistention of the healthy lung." But if such be the explanation, how can a healthy and elastic lung displace the solid pneumonic lung which "fills the greater part of the pleural cavity?"

6. The roentgenographic findings in experimental pneumonia in dogs. In these cases, as we have already shown in previous papers,<sup>14, 15, 16</sup> the picture is strikingly similar to that of experimental atelectasis in the dog. The same displacement of the heart and the trachea to the affected side and the same elevation of the diaphragm to the affected side are present. Figs. 1, 2, 3 and 4 offer a clear demonstration of this fact. Moreover, independently of any theoretical discussion, it is easy to demonstrate these facts by autopsying a pneumonic dog, killed with chloroform or intravenous injection of formalin. It is necessary to avoid the use of ether because of rapid diffusion of this gas through the surface of the lung after opening of the chest with subsequent rapid collapse of the healthy lung. Before the chest is opened the trachea is dissected free and carefully clamped; in opening the chest by section of the sternum, the healthy lung will appear much more voluminous than the affected one, which will be easily recognized by its bluish-black color, and will lie deep down in the thoracic cavity (Fig. 5). In favorable cases of total pneumonia of one lung, particularly the right, the heart will clearly appear displaced toward the affected side. If, now, we release the clamps on the trachea we see that the healthy lung rapidly collapses, and appears smaller than the affected one.\* We verified these findings at autopsy of a man, aged sixty years, who died on the sixth day of the disease with pneumonia of the entire right lung. We first clamped the trachea and then opened the chest. The left (healthy) lung appeared larger than the right, and the impression was verified by obtaining the water displacement of the affected lung. It is necessary to proceed rapidly and avoid manipulation of the healthy lung, because of the rapid diffusion of the alveolar air through its surface. Another suggestion for testing the true size of the respective lobes in the human is as follows: Into the trachea of the cadaver is inserted a cannula connected by a small rubber tube to

\* This experiment was shown at the meeting of the New York Pathological Society, Academy of Medicine, January 10, 1929.

a water manometer. The chest is then opened, care being taken to avoid injury to the lungs. A positive pressure now registers on the manometer and is a measure of the elastic recoil of the lungs which collapsed because the negative intrapleural pressure was eliminated by opening the chest. If we now enclose the lungs in an air-tight chamber, the trachea protruding, and decrease the pressure within this air-tight chamber so as to bring the manometer reading back to zero, the true size of the lobes will be depicted; or else air may be insufflated into the trachea at a pressure equal to the

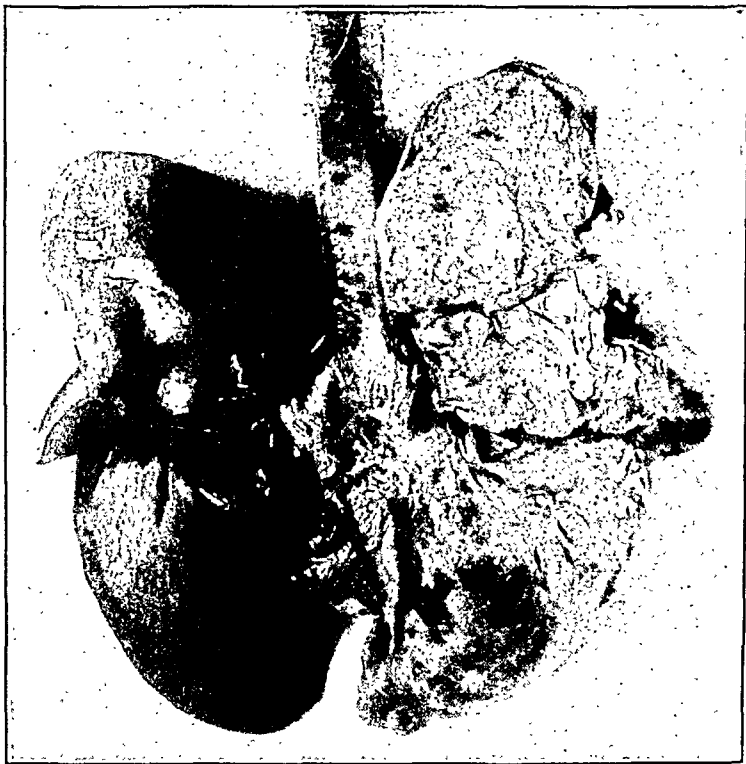


FIG. 5.—Lobar pneumonia of the left lung in a dog. The trachea was clamped before opening the chest in order to preserve the true-size relations. The left (consolidated) lung (blackish) is smaller than the right. When the clamp was released the healthy lung collapsed to a smaller size than the pneumonic lung.

positive pressure originally shown on the manometer, for this method will also restore the lobes to their true intrathoracic size before the chest was opened. It is evident that both methods described act by distending only the healthy lobes, and in this way alone is an increase in the size of the lung effected.

In studying the circulation in the consolidated lung in pneumonic dogs<sup>17</sup> we were surprised to find that in the earliest stages of lobar pneumonia the alveoli are shrunken. This study was carried out by injecting in the living animal a solution of india ink (20 per cent) in Ringers' solution, through the proximal end of the jugular vein, the distal end of which was left open to allow outflow of blood. Repeating the same injection in dogs in which atelectasis of one

lung was artificially induced by occluding a bronchus with our balloon, we found exactly the same picture. In more advanced periods of the conditions the circulation is more markedly impaired in both pneumonia and atelectasis.

From the above facts we conclude that the affected lobes in lobar pneumonia are smaller in size than the healthy ones. This explains the absence of displacement of the mediastinum to the sound side; the elevation of the diaphragm in the affected side, which is due to the "suction" exerted upon it because of the decrease in the size of the corresponding lung. The elevation of the diaphragm is to some extent directly related to the rigidity and the resistance which the mediastinum offers to being displaced. When the mediastinum yields easily, as in dogs or very young children, the elevation of the diaphragm will be less. This displacement of the mediastinum (heart and trachea) to the affected side, especially in children, which has so often been reported, and considered "paradoxical and inexplicable" is very easily accounted for by the above conception.

There is no doubt that this mediastinal displacement in pneumonia in the human being is much less pronounced than in atelectasis. We think this is due to two facts: (1) That in atelectasis there is little exudate in the alveoli, whereas in lobar pneumonia a rapidly developing exudate fills the alveoli, thus preventing their complete shrinkage; (2) that in massive atelectasis generally the whole lung of one side is affected, whereas in lobar pneumonia generally one lobe or even a part of it only is involved. Therefore, in comparing the displacement of the mediastinum in atelectasis and pneumonia we must consider cases in which equal and comparable areas of lung are involved.

**Conclusions.** 1. The size of the affected lobes in lobar pneumonia, contrary to the generally accepted opinion, is smaller than that of the healthy lobes. The enlargement of the consolidated lung is only apparent and is due to the collapse of the healthy lung when the thoracic cavity is opened.

2. In order to appreciate the true sizes of the consolidated and healthy lobes it is necessary to clamp the trachea and then to open the chest with only the minimum manipulation of the healthy lobes.

3. The decreased size of the pneumonic lobe, as shown by Roentgen ray and postmortem studies, points to a similar pathogenesis in pneumonia and atelectasis.

4. The above points definitely proven for the dog need further confirmation for the human being.

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## CARCINOMATOUS ABSCESS OF THE LUNG.

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THE pathologist and, especially, the clinician think of pulmonary excavations as most commonly due to tuberculosis and, next in frequency, to abscess or gangrene due to various etiologic factors. In our study of the pathology and clinical history of neoplastic disease of the lung we have encountered a fairly large number of cases in which the dominant clinical picture was that of pulmonary excavation, simulating pulmonary abscess, tuberculous disease or bronchiectasis. In some, the necropsy showed the gross pathology of lung abscess and only after a microscopic study of its wall were we convinced that we were dealing with malignancy terminating in gangrene of the neoplastic tissue which was expelled, leaving an excavation. While we have met with many allusions to this form of neoplastic disease of the lung in pathologic literature, very few clinicians have recognized it during the life of their patients. In another communication

one of us has given some details of the cavity-producing type of neoplasm of the lung. Here we intend to report a group of 15 cases which came to necropsy. Inasmuch as cavities were found in 15 of 51 cases of primary cancer of the lung that came to autopsy at the Montefiore Hospital, it appears that about 30 per cent of lung neoplasms partially break down, are expelled by cough and leave cavities.

These cancerous cavities may be of various sizes. In rare instances an entire lobe may be destroyed; others are of the size of a large orange, while some are quite small. In some their differentiation from tuberculous, gangrenous or bronchiectatic cavities presents no difficulties to an experienced pathologist; in rare cases it is difficult to establish the malignant etiology until a careful microscopic study is made of the wall and adjacent tissues of the cavity. In nearly all cases we found a large thickened bronchus communicating with the cavity, draining the purulent material and detritus of necrotic tissue which may be found in fairly large lumps. It is noteworthy that in some cases the growth proliferates in the upper lobe of the lung, but for quite some time the interlobar fissure prevents its spread downward, a point best observed in roentgenograms.

The gross appearance of the necrotic tumor may resemble that of fibrocaseous pulmonary tuberculosis and the surrounding tissue usually presents an inflammatory area. Further on toward the periphery, there may be vicariously emphysematous lung tissue, but more often, owing to occlusion of the supplying bronchus, atelectasis of the alveoli is encountered. In some cases we observed massive atelectasis of a lobe because of complete obturation of the supplying bronchus. In several cases, concomitant active tuberculous lesions were found, while fibrotic changes of the apical pleura due to old tuberculosis are quite common. In one case we found an old, smooth-walled tuberculous cavity in close proximity to the large cancerous cavity. Microscopic study of another revealed miliary tubercles surrounding the wall of a cancerous cavity.

Metastatic deposits in other organs are as common as in cancer of the lung without excavation and have been discussed in another place by one of us.

It is noteworthy that excavation occurs mostly in primary tumors of the lung. In metastatic tumors it is rather uncommon: We may find large masses of secondary tumor deposits in both lungs, lasting for months without breaking down.

Excavation of a pulmonary neoplasm may be the result of purely mechanical factors: The tumor mass, growing rapidly, outgrows its blood supply and anemic necrosis of the central part ensues, the necrotic tissue being eliminated through the communicating bronchus. In such cases, however, it is usually the result of superinfection with pyogenic microorganisms and occasionally with spiro-

chetes and spirillæ which are the pathogenic agents in many forms of pulmonary suppuration without malignancy.

**Symptomatology.** Elsewhere one of us described in detail the clinical phenomena of cancer of the lung, showing that in the vast majority of cases it can be diagnosed much earlier than current medical literature would lead us to suppose. The cavity form, however, presents some special features which will be discussed here.

In the cases in which the excavation appears late in the course of the disease, especially after the diagnosis of cancer of the lung has been established, the recognition of the cavity may be merely of academic interest. But we meet many others in which the first symptoms are those of gangrene or abscess of the lung, at times of pulmonary tuberculosis, and in these an error in diagnosis may prove rather serious. They are either referred to sanatoriums for treatment, banished to some distant climatic resort, or diagnosed as abscess and subjected to surgical treatment. We met with several of the latter group. In one the surgeon did not recognize the malignant underlying process while operating and only at the necropsy was the clinical diagnosis of cancer confirmed.

In most cases, the symptoms are those of cancer of the lungs. The patient, of the cancer age, has been coughing for several weeks or months, has pain in the chest, hyperesthesia of the chest wall and is dyspneic even without exertion. Pain and hyperesthesia of the chest wall and pronounced dyspnea are very rare in tuberculosis or lung abscess unless there is concomitant acute pleurisy or pneumothorax. There is elevation of temperature in nearly all cases, even in those that began insidiously. In some cases the history is that of a sudden onset with chill and high fever and for that reason the diagnosis of pneumonia is made. If the sputum is fetid from the start, lung abscess is diagnosed. The fever may then be high and continuous, reaching 103° or even exceeding 105° F., but the crisis does not appear within a reasonable time. In others the fever is intermittent in type, and there may be repeated chills, followed by a rise in the temperature, culminating in profuse sweating. The expectoration is usually copious, often very fetid and mixed with blood. Profuse hemorrhage may take place at any time in the course of the disease and frequently proves fatal. Six of the 15 cases reported here died from pulmonary hemorrhage.

Those unacquainted with the physical signs of cancer of the lung make confidently a diagnosis of abscess of the lung, especially in cases with more or less insidious onset. But a discriminating physical exploration of the chest usually reveals the true nature of the underlying malignant process. It will be found that over a localized area of the affected side of the chest wall, usually the upper lobe and in some over the lower lobe, the note elicited by percussion is flat, a characteristic which is rarely found in lung abscess, or in pneumonia, unless there is a concomitant pleural effusion. On

auscultation, the breath sounds are found to be either completely suppressed over the site of the flatness, or very feeble. In most cases adventitious sounds are not audible, but after the tumor has broken down, large, moist and bubbling râles make their appearance. When this stage is reached, one may obtain distant cavernous or blowing breath sounds.

In many cases the changes noted on the Roentgen ray film are not characteristic, but may be not unlike those seen in tuberculosis, abscess, bronchiectasis, and so forth. There is one type, however, which is very characteristic of a malignant abscess: There is a circular shadow which may be several inches in diameter, partly filled with fluid which may be seen to shift under the fluoroscope when the patient's position is changed. The capsule may be very thin, though at one side it is almost invariably thickened. Cases XII and XIII were of this character. In some cases the circular shadow may be homogenous, clearly showing that we are dealing with a new growth or a cyst. But in the majority, the roentgenogram, taken without the clinical history and the physical signs, cannot be relied on for conclusive diagnosis. In suspicious cases, the fact that the lesion is clearly unilateral may be taken to speak against tuberculosis; but this also is subject to many exceptions.

Occasionally the laboratory findings may help. In cases with pleural effusion sedimentation of the fluid, cutting sections of the sediment and examining microscopically has at times been of assistance. In a few, the sputum showed highly degenerated cells which gave a clue, but this also is exceptional because of the peculiar cytology that may be found in sputum derived from patients with other diseases. In some the bronchoscopist was of assistance. But now and then the specimen removed through the bronchoscope showed cells not unlike those seen in malignancy, yet the course of the disease showed that there was no neoplastic condition.

**Case Reports.** The following cases illustrate the clinical findings:

CASE I.—D. Z., a man, aged sixty years, admitted January 18, 1923, had pain in the chest for four years, cough, expectoration, slight hemoptysis, weakness and night sweats. Ten months prior to admission he sustained a blow on the chest which made him lose consciousness and spit blood. Following this accident, he began to raise considerable purulent sputum with a fetid odor, and hemoptysis became common. Physical examination of the chest revealed flatness over the right upper lobe and distant cavernous breath sounds below that area. Over the lower lobe of the left lung flatness and absence of breath sounds were found. On the roentgenogram a small localized pneumothorax was discovered which apparently was caused by an exploratory puncture. Because of these findings, chronic pulmonary tuberculosis was diagnosed and he was sent to our tuberculosis wards. But despite the large quantities of sputum available, no tubercle bacilli could be discovered on repeated examinations. There were, however, found masses of highly degenerated cells which were considered malignant in origin. On March 25, 1923, he suddenly succumbed to a copious and uncontrollable hemorrhage. The necropsy revealed a carcinoma of the



right lung, primary in the bronchus with metastasis to the regional lymph nodes, pleura, left lung and liver. There were several cavities in each lung, the largest in the right upper lobe, measuring 5 cm. in diameter.

CASE II.—S. C., a man, aged forty-six years, admitted May 22, 1922, with a history of cough and blood-tinged sputum for two years. He had pain and hyperesthesia over the right side of the chest and was severely dyspneic. He stated that he never had fever. For a few months prior to admission he had had several copious pulmonary hemorrhages; during his stay in our wards he had daily mild hemorrhages and the sputum became very copious and offensive in odor. The physical signs were flatness of the upper lobe of the right lung and feeble breath sounds combined with large, moist consonating râles. Repeated examinations of the sputum failed to show the presence of tubercle bacilli, but spirochetes and fusiform bacilli were found in large numbers. On the Roentgen film, a dense shadow was seen over the site of the right upper lobe, while the left lung was apparently free from pathologic changes. Finally, the pulmonary hemorrhages became more and more copious and on February 10, 1923, he succumbed to exsanguination. At the necropsy, a squamous-celled carcinoma of the right upper lobe bronchus with gangrene was found, leaving a large excavation.

CASE III.—M. G., a man, admitted January 23, 1928, had had cough and pain in the chest for eighteen months. The pain and hyperesthesia in the left chest of late became very severe and radiated to the shoulder and the lower dorsal spine. For a year the cough had been productive of considerable sputum which of late had become fetid. The usual physical signs were found on the left side of the chest. On the Roentgen film, a large irregular shadow the size of an apple was seen extending from the hilus to the periphery with a bright area in the center. There was found also a slightly enlarged glandular nodule in the region of the left thyroid. Removal of a specimen through the bronchoscope was done and microscopically cancer cells were discovered. Several Roentgen treatments were given to this patient but the course continued downward, the cough was aggravated, and sputum increased in amount, was blood tinged and the pain became unbearable. He succumbed on March 10, 1928, to a pulmonary hemorrhage. At the necropsy the left upper lobe was found completely replaced by a carcinomatous growth, the greater part of which was gangrenous and excavated; spirochetal pneumonia of the left lung was also revealed. There were found metastatic deposits into the thyroid and adrenals.

CASE IV.—G. C., a woman, aged fifty-four years, admitted January 14, 1924, had been coughing for one year and had severe pain in the right chest. Because of the cough and several attacks of hemoptysis, emaciation and fever, she was sent into our tuberculosis wards. Physical examination showed flatness over the entire right lung, from apex to base, feeble breath sounds over the upper half and absence of all breath sounds over the lower half. On the Roentgen film was seen a dense homogenous shadow occupying the upper half of the right side with a clearly delimited lower border. Exploratory puncture revealed a serosanguinous effusion in which were found cancer cells microscopically. She died from a pulmonary hemorrhage on January 15, 1915. The necropsy revealed a carcinoma occupying the upper half of the right lung with a large cavity in the center.

CASE V.—I. K., a man, aged sixty-three years, admitted March 2, 1916, had been losing in weight and strength for more than a year prior to admission. Three months ago he suddenly began to feel excruciating pain in the left shoulder, axilla and pectoral region, paroxysmal cough, productive of

bloody sputum and dyspnea. Physical examination of the chest revealed hyperresonance over both sides, excepting the left upper lobe where the note was dull both anteriorly and posteriorly, and respiratory murmur was feeble. No adventitious sounds could be heard at that time. The Roentgen film showed a dense homogeneous shadow above the fourth rib, and another similar shadow at the left base. An exploratory puncture brought out serosanguinous fluid from the left pleura. It is noteworthy that a Roentgen film taken one year prior to admission showed that the lungs presented no pathologic changes, while another film taken four months prior to admission showed only a shadow over the left apex, but no fluid in the pleura. He died April 6, 1916. At the autopsy, there was found a squamous-cell carcinoma occupying the upper third of the left lung, with a cavity in its center. Microscopic examination showed several fresh tubercles within the pneumonic patch surrounding the tumor.

CASE VI.—E. C., a man, aged sixty-three years, admitted May 19, 1922, for eighteen months had been coughing, and more recently had pain in the left chest and shoulder, weakness and severe dyspnea. The cough had been severe, incessant and productive of large quantities of fetid sputum. Pulmonary hemorrhage of moderate degree occurred several times. More recently, he had difficulty in swallowing and became hoarse. He had been treated for lung abscess in another institution. The physical exploration of the chest showed the usual unmistakable signs, flatness over the left chest from apex to base, feeble breath sounds and large moist râles over the upper half. On the Roentgen film a dense homogeneous shadow was found across the left chest about 3 inches in width, while the lung tissue above and below that shadow was poorly illuminated, indicating compression atelectasis. An exploratory puncture brought out serosanguinous fluid in which were found microscopically cancer cells. Death occurred July 9, 1922. At the necropsy, the left lung was found invaded by a carcinomatous growth with metastatic deposits in the peribronchial lymph nodes and extension into the chest wall. A large cavity was found in the upper lobe.

CASE VII.—A. R., a man, aged sixty-four years, was admitted December 6, 1927, and died two weeks later. He had coughed for one year, had pain in the chest and dyspnea. Expectoration was profuse and fetid but he never had hemoptysis. Of late, he had been losing considerably in weight. At no time had he had fever, and the course in the hospital was entirely afebrile. Physical exploration of the chest revealed the usual signs of a neoplasm involving the entire right lung. On the Roentgen film there was noted a dense shadow on the right side extending from the apex to the base. Several hundred cubic centimeters of serosanguinous fluid was removed by thoracocentesis and then a new film taken, but this also was not conclusive unless correlated with the history and physical signs. At the necropsy there was found a carcinoma, which had undergone cavitation, occupying the entire upper lobe of the right lung, and metastatic nodules in the regional lymph glands. Here again the diagnosis, based on the history and the flatness from apex to base, was more reliable than the Roentgen film.

CASE VIII.—H. H., a man, aged forty-eight years, admitted March 11, 1919, dated his troubles back to a fracture of the right heel in September, 1918. But at that very time he also had pain in the sacral region. Of late, he had been having severe coughing spells, productive of purulent and blood-tinged sputum with a fetid odor. He had lost considerably in weight and strength and has been severely dyspneic. Physical examination of the chest elicited over the right lung signs similar to those in the preceding case. So did the Roentgen examination. Metastatic deposits of the neoplastic

tissue were discovered roentgenologically and clinically in various parts of the skeletal system. Thoracocentesis revealed a serofibrinous effusion in the right pleura. Death occurred April 12, 1919, with evidence of cerebral metastasis. At the necropsy, there was found a squamous cell carcinoma of the right lung with a large excavation at the junction of the upper and middle lobes. There were numerous metastatic deposits in the osseous system and the abdominal viscera.

CASE IX.—K. R., a man, aged sixty-two years, was admitted April 11, 1916, with a history of fever seven months previously. Following this fever, which lasted several weeks, he began to cough, expectorate fetid sputum and lose in weight and strength. Of late, the most annoying symptom had been dyspnea. At no time had he noted any blood in his expectoration. Physical examination revealed flatness over the right upper lobe and feeble breath sounds. Roentgen examination revealed a homogeneous shadow covering almost the entire upper lobe of the right lung, with bright areas suggestive of excavation in that region. A film made six days later showed a fluid level in one of the cavities. The sputum was consistently negative for tubercle bacilli. Three months later he developed a soft, tender nodule above the right clavicle. He died suddenly September 7, 1916. At the autopsy, there was found a squamous-cell cancer the upper lobe of the right lung with extensive cavity formation. There was a direct extension of the tumor to the thoracic vertebræ, the right clavicle and the regional lymph glands.

CASE X.—J. S., a man, aged fifty-two years, admitted June 1, 1922, had been coughing for twenty years and expectorated profusely a foul-smelling material occasionally blood-tinged. He got along fairly well until about six months prior to admission when his cough and expectoration became more severe and he began to experience severe pain in the right side of the chest and, coincidentally, to suffer from severe dyspnea. Physical examination of the chest disclosed flatness on percussion over the upper third of the right chest and diminished breath sounds of a bronchial character. On the Roentgen film, the entire upper lobe of the right lung appeared as a dense homogeneous shadow delimited sharply below at the site of the interlobar fissure with a bright area in its upper third. He died suddenly July 9, 1922. At the necropsy, the right upper lobe was found invaded by a carcinoma with a large excavation in the center.

CASE XI.—A. H., a man, aged thirty-nine years, admitted March 22, 1915, had coughed for a year, expectorated blood, lost in weight and felt weak. He complained mainly of a sharp pain in the left chest, radiating down to the left lower extremity. Of late, the expectoration had become more profuse, bloody and fetid. He lost 35 pounds in weight. The physical signs were those commonly found in lung malignancy. Excision of a palpable axillary lymph node showed on microscopic examination adenocarcinoma. The fever increased and during the last two weeks of life reached 105° F. Death occurred May 12, 1915, with symptoms of terminal pneumonia. At the necropsy, an adenocarcinoma was found occupying the entire left lung with a large cavity in the upper lobe. Metastatic deposits were found in the right lung, in the bronchial, cervical, axillary, mesenteric and retroperitoneal lymph glands and in the liver.

CASE XII.—N. B., a man, aged sixty-five years, admitted June 1, 1922, had been coughing for many years and was short-winded, but this was easily explained by the advanced pulmonary emphysema. However, the onset of the present illness was rather sudden, with severe pain under the left scapula, cough, purulent expectoration which was frequently stained with blood and at times fetid. Within a year he lost 33 pounds in weight. The physical

signs obtained were those of pulmonary emphysema excepting for dullness found in the left interscapular space. No adventitious sounds were heard. The skin over the upper half of the left chest was very sensitive to touch. Roentgen examination revealed in the left lung a bright, round area, the size of an apple, clearly delimited and half filled with fluid, which shifted on motion of the patient. This bright area was surrounded by a dense capsule. The sputum though very abundant, was always found negative for tubercle bacilli. He ran a temperature oscillating around  $101^{\circ}\text{F.}$ , but toward the end it rose much higher. He died August 14, 1922. At the necropsy, there was found within the emphysematous lung a large, round cavity in the upper lobe of the left lung which could not be explained etiologically on gross appearance. Only a microscopic study of the wall of the cavity showed that we were dealing with a squamous-cell carcinoma which had broken down and had almost completely been eliminated by expectoration.

CASE XIII.—H. B., a man, aged sixty-eight years, admitted September 24, 1924, had a history similar to the preceding. For four years he had been having severe pain in the left chest, paroxysmal cough productive of foul-smelling and bloody sputum. Lung abscess was diagnosed and a therapeutic pneumothorax was induced in another hospital. But he continued downward, and he was transferred to the Montefiore Hospital. The physical signs were those of cavitation in the middle third of the left lung. But recalling the preceding case, and the hyperesthesia of the skin over the left side of the chest, the dilated veins over that region and the cachexia, a diagnosis of malignancy was made. Repeated examination of the sputum failed to disclose the presence of tubercle bacilli or cancer cells. Roentgen examination revealed a large, round cavity in the middle of the left lung, filled partly with fluid, partly with air. Giving this patient a large dose of opiate so that he slept through the night resulted in the secretion filling up the cavity, while emptying the cavity was often accomplished by withdrawal of opiates and postural drainage. Six weeks later we found evidences of metastasis in other parts of the lung. Death occurred February 2, 1925, as a result of exsanguination through an uncontrollable pulmonary hemorrhage. At the necropsy there was found a squamous-cell carcinoma of the left lung with a large cavity in the center, filled with clotted blood. There were metastases to the chest wall, pericardium and regional lymph glands.

CASE XIV.—S. F., a woman aged forty-three years, admitted May 1, 1927, had been sick for three years. She had coughed and expectorated profusely foul-smelling material, at times tinged with blood. Prior to admission to Montefiore, a thoracocentesis was performed and some serous fluid was removed from the left pleural sack. An exploratory puncture done in our wards revealed purulent material. Physical examination of the chest showed signs common in far-advanced bilateral pulmonary tuberculosis with cavitation in both lungs, and fluid in the left pleura. Roentgen ray examination showed extensive areas of consolidation scattered throughout all the lobes with numerous excavations. Sputum was repeatedly negative for tubercle bacilli. The course was progressively downhill with marked asthenia, uncontrollable cough and fever reaching  $103^{\circ}\text{F.}$  She died July 15, 1927. At the necropsy the gross anatomic findings were rather peculiar, simulating tuberculosis. Microscopic study, however, revealed an adenocarcinoma of both lungs with several excavations. No metastases could be discovered.

CASE XV.—M. S., a man, aged fifty-one years, admitted May 6, 1925, began fifteen months prior to admission to cough up blood. These symptoms persisted for four months when he began to experience pain in the left chest. He lost considerably in weight. Three months prior to admission his left side of the chest began to bulge. A diagnosis of empyema was made and he was operated upon, but the wound failed to heal and he was

sent into the wards of the Montefiore Hospital. On physical examination, we found, as is common in these cases, flatness over the left side of the chest from apex to base and complete absence of breath sounds. The Roentgen ray picture showed a homogeneous shadow all through the left half of the chest. The patient gradually lost in weight and strength, continued to expectorate foul-smelling material which was of the same character as that discharging from the operative wound. He died within a month after admission. The necropsy revealed an alveolar-cell carcinoma of the left lung with gangrene and abscess formation. There were metastases to the ribs, bronchial and axillary glands and liver.

**Comment.** It appears that malignant disease of the lung, which of late has become very common, is apt to manifest itself with symptoms and signs of abscess and gangrene of the lung. While in persons under thirty-five years of age tuberculosis, bronchiectasis and abscess of the lung are the more common diseases to be thought of when a patient coughs, bleeds, has fever and loses in weight, in persons of the cancer age, these symptoms often denote malignancy of the bronchi or lung. The etiologic differentiation is very important if only because we may thus avoid advising these patients to seek climatic or other forms of antituberculosis treatment, or operative interference when pulmonary abscess is erroneously diagnosed. And the diagnosis of malignant abscess of the lung can be made in the vast majority of cases.

Tuberculosis can be excluded, bearing in mind the following points: No tubercle bacilli are found in the sputum despite its abundance. Fetid sputum is very rare in tuberculosis, unless gangrene of the lung is superimposed, but this occurs very rarely only, and then we have a history of tuberculous disease for many months or years prior to the appearance of fetid sputum. Extensive tuberculous disease of the lung is very rarely unilateral, while in primary cancer this is the rule and only in the terminal stages may metastatic deposits be found in the contralateral lung. Severe pain, and especially hyperesthesia of the chest wall, is not common in tuberculosis unless pleurisy complicates the process, while in malignancy it is present in over 90 per cent of cases, and its severity is such as is hardly ever seen in tuberculosis. Likewise, dyspnea is not common in tuberculosis, unless there is a complicating pleural effusion, or a pneumothorax, or in the terminal stages of fibroid phthisis. But in cancer it occurs very early and may, with the pain and cough, be the main symptom that brings the patient to seek medical advice. The physical signs also point to malignancy when we bear in mind that a flat note on percussion of an apex is hardly ever obtained in tuberculosis, while in cancer of the upper lobe it is the rule. A tuberculous pleural effusion hardly ever manifests itself in flatness on percussion of the side of the chest all the way down from the apex to the base, while in malignant effusions this is the rule. Careful study of the cytology of the sputum and pleural exudates may reveal cancer cells.

It is often very difficult to differentiate malignant abscess from abscess and gangrene of the lung due to other causes. Of course in persons under thirty-five years of age cancer of the lung is even rarer than malignancy of other organs. But abscess of the lung often occurs in persons over thirty-five years of age with or without any assignable etiologic factor. However, in a large proportion of cases of abscess of the lung we do find some cause, such as tonsillectomy, extraction of teeth, or surgical operations on the jaws, especially in diabetics, or after operations under general anesthesia. Abscess following bronchopneumonia, particularly of the influenzal type, is also easily diagnosed by the history and course of the disease. On the other hand, we have shown that it is not uncommon that cancer of the lung shows its first clinical manifestations with symptoms and signs not unlike those of pneumonia which fails to resolve or otherwise terminate. But in the majority of cases of cancer of the lung the onset is insidious with cough, expectoration often foul, hemoptysis, pain in the chest and hyperesthesia, and sooner or later, fever. In these cases, the physical signs described above, as well as repeated roentgenograms will clear up the diagnosis.

**Summary.** Fifteen cases of primary cancer of the lung are reported in which clinically and at the necropsy table excavations were found. It appears that about one-third of the cases of neoplastic disease of the lung break down, leaving a cavity after the necrotic tissue is eliminated.

It is emphasized that such patients with excavated carcinoma of the lung often present the seemingly typical symptomatology, physical signs, and even roentgenoscopic appearance of abscess of the lung. In fact, the simulation of the clinical picture of pulmonary abscess may last for many months. In all instances of apparently primary abscess of the lung of recent onset in elderly individuals, the possibility of broken-down neoplasm is to be borne in mind.

## A CASE OF DIABETES MELLITUS SHOWING AGLYCEMIA WITHOUT SYMPTOMS.

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CASES of diabetes mellitus showing hypoglycemia without symptoms have previously been reported.<sup>1</sup> As far as the writers have been able to ascertain, the case reported here is the first record

of a patient whose blood, following the administration of insulin, showed no glucose whatever and at the same time there were no clinical signs nor symptoms to suggest the condition.

**Case Report.** R. B., a male, aged twenty-two years, was admitted to The Montreal General Hospital on October 7, 1928, complaining of drowsiness, considerable thirst, hunger and obstinate constipation.

The family history is irrelevant.

The personal history is also irrelevant with the exception of an attack of influenza in 1922 for which he was in bed two weeks, and an attack of scarlet fever during the latter part of the same year.

The present illness apparently dates back to 1924 when he noticed that he was drinking large quantities of water. This was the only complaint then. One year later, he noticed a marked craving for food. In spite of this he did not consult any physician until one year later when the diagnosis of diabetes mellitus was made. He was then put on a diet and continued to work for several months, but eventually had to stop. He stated that he received insulin during the last year but has been irregular in his habits both as to diet and insulin. Two weeks before his admission to the hospital he again consulted his physician who advised immediate intensive treatment.

On admission, the findings of the physical examination were negative with the exception of an obvious state of undernutrition and a marked acetone odor to the breath. He then weighed 108 pounds. The urine contained no albumin nor casts, but had large quantities of sugar, acetone and diacetic acid. The blood sugar in the fasting state was 0.385 per cent and the plasma cholesterol was 0.230 per cent.

The other laboratory findings were as follows: Urea nitrogen, 25 mg. per 100 cc. of blood; creatinine, 1.57 mg. per 100 cc. of blood; Wassermann, negative; Roentgen ray of chest, negative; routine Roentgen ray of both feet in order to detect calcification of arteries, negative; fundi, negative.

In view of the clinical and laboratory findings, insulin treatment was immediately instituted. The diet at first was low, both as to carbohydrates and caloric content. It was, however, gradually increased daily and on October 17 he was receiving a diet consistent with his energy requirements. It then consisted of 50 gm. carbohydrates, 150 gm. fat and 50 gm. protein. On this diet, however, the glycosuria though mild, was persistent. The urine contained 3 to 5 gm. of sugar per day. Acetone bodies were still present, and the daily blood sugars, in the fasting state, ranged between 0.250 and 0.322 per cent. Clinically there was definite improvement.

It is obvious from the above findings that, in spite of the clinical improvement, the diabetes was not under ideal control. The insulin dosage was then increased and on October 28, he was receiving 90 units a day. In spite of this, the laboratory findings remained unaltered. The urine still contained traces of sugar and acetone bodies and the blood sugar in the fasting state was 0.320 per cent.

The possibility was then considered that the patient is, what we now recognize as, an "insulin waster;" that is, in some cases in spite of large doses of insulin before meals sufficient to produce reactions after meals, the fasting sugars the following morning still show hyperglycemia. An attempt was then made to readjust the dosages of insulin. For this purpose, the urines were partitioned as follows: 8 A.M. to 12 noon, 12 P.M. to 5 P.M., 5 P.M. to 10 P.M., 10 P.M. to 7 A.M. and 7 A.M. to 8 A.M.

It will be seen that, by the above procedure, it was possible to study the sugar contents of the urines in relation to breakfast, lunch, dinner, night metabolism and metabolism of the fasting state. This showed that glyco-

suria made its appearance during the night period, that is, from 10 P.M. to 7 A.M. The insulin dosage was readjusted on this basis, but in spite of this the morning fasting hyperglycemia could not be overcome. In view of this it was considered advisable, because of past experience with similar cases, to administer insulin, not in relation to the meals, but at regular intervals throughout the twenty-four hours. By this procedure, it is frequently possible to reduce the dosage of insulin and at the same time increase the diet and keep the urine free of sugar. In this case by giving 10 units of insulin every six hours, it is possible to keep the urine free of sugar and acetone bodies and maintain a normal blood sugar in the fasting state. That is, 40 units of insulin a day is able to accomplish that which 90 units, previously given in relation to meals, failed to.

The further history was uneventful until October 30, when he had a severe reaction manifested by a complete hemiplegia similar to that seen following cerebral hemorrhage. With the use of orange juice, the hemiplegia disappeared the same day and for the following two days there was some muscular weakness on the affected side. This has now entirely disappeared.

On the morning of November 1, the fasting blood obtained as a routine showed a sugar content of 0.026 per cent. At that time there were no clinical signs nor symptoms whatever to suggest hypoglycemia. (It may here be stated that the possibility of technical error in the determination of blood sugar was excluded.) Another determination made at noon on the same day showed a blood sugar of 0.059 per cent, and the following morning it was 0.040 per cent. It is obvious, therefore, from the above findings, that the patient not only had hypoglycemia, but at one time had practically no glucose whatever in the blood, if we take into consideration the fact that the 26 mg. which were present correspond fairly closely to the average amount of nonfermentable (that is, nonglucose) reducing substances in human blood.

In order to determine the actual degree of hypoglycemia possible without symptoms, in this case, the following observations were made.

On November 21 the blood sugar in the fasting state was normal (0.095 per cent) and the urine was free of sugar. He was then given 10 units of insulin but no breakfast nor any food until 5 P.M. the same day. (There were no reactions during this period of observation.) Sugar determinations were then made hourly, both before and after fermentation, with the different blood specimens. The technical details for this purpose were those previously reported (2) and for purpose of brevity are not described here. The results are shown in the following table:

BLOOD SUGAR (PER CENT).

Period.	Fermentation.		Differences.
	Before.	After.	
8.00 A.M. . . . .	0.095	0.026	0.069
9.00 A.M. . . . .	0.064	0.023	0.041
10.00 A.M. . . . .	0.028	0.027	0.001
11.00 A.M. . . . .	0.025	0.026	
12.00 NOON . . . . .	0.023	0.024	
1.00 P.M. . . . .	0.027	0.025	0.002
2.00 P.M. . . . .	0.028	0.026	0.002
3.00 P.M. . . . .	0.027	0.024	0.003
4.00 P.M. . . . .	0.031	0.026	0.005

It will be seen from the above data, there is definite evidence that during a period of six hours, that is, from 10 A.M. to 4 P.M. there was no glucose whatever in the blood, and as just stated there were no



reactions. The few milligram differences recorded, with the exception perhaps of that of the 4 o'clock specimen, are not regarded as significant, since they correspond to the limits of experimental error inherent in the technical methods employed.

An interesting observation is that when the patient returned to the ward from the laboratory he was given his routine 10 units of insulin at 5 o'clock, that is, one hour after the blood sugar was 0.031 per cent and the glucose content only 0.005 per cent, and again no signs nor symptoms followed suggesting an insulin reaction.

**Summary.** A case of diabetes mellitus showing aglycemia without symptoms is reported. Absence of glucose in the blood after the administration of insulin was proven by the determination of the reducing substances of the blood before and after fermentation. In view of repeated observations by other authors of hypoglycemia without symptoms, and in view of the present case, it is suggested that though hypoglycemia is an important factor, probably the most important, in the production of the train of symptoms following an overdose of insulin, it is probably not the only factor involved.

NOTE.—The writers are indebted to Dr. A. R. Landry of Moncton, N. B., who referred this patient for observation.

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## COMPLICATIONS AND FATALITY OF TYPHOID FEVER AMONG FILIPINOS.

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**Introduction.** This investigation was made to study the complications and fatality of typhoid fever among Filipinos. Our study covers all the cases of typhoid fever admitted to the Philippine General Hospital since the establishment of this institution in September, 1910. Fifteen cases admitted during the early part of the operation of the hospital were excluded because of incomplete records. Our investigation, therefore, extended from January, 1911, to October, 1927, a period of almost seventeen years, and comprised a total of 3255 cases with complete and comprehensive records.

**Sex and Age Distribution.** *Sex.* Our series included 2046 males and 1209 females, showing a marked predominance of males.

*Age.* 2547 cases or 78.29 per cent of the entire total of the series, occurred between the ages of eleven to thirty years, with a gradual diminution after the third decade.

Graph I shows the percentage distribution by age groups of our cases as compared with those of Curschmann. The greatest incidence occurred in the age groups of eleven to twenty and twenty-one to thirty years. We found a higher percentage distribution than Curschmann in the first two decades of life, but less in the third and fourth.

TABLE I.—PERCENTAGE DISTRIBUTION OF CASES OF TYPHOID FEVER ADMITTED TO THE PHILIPPINE GENERAL HOSPITAL FROM JANUARY, 1911, TO OCTOBER, 1927, INCLUSIVE, BY AGE GROUPS COMPARED WITH CURSCHMANN'S DATA.

Ages.	Our cases.		Curschmann.	
	Cases.	Per cent of total.	Cases.	Per cent of total.
1 to 10 . . . . .	305	9.37	206	5.62
11 to 20 . . . . .	1377	42.30	1345	36.66
21 to 30 . . . . .	1170	35.95	1594	43.45
31 to 40 . . . . .	296	9.09	396	10.79
41 to 50 . . . . .	71	2.18	107	2.91
51 to 60 . . . . .	26	0.80	21	0.57
61 to 70 . . . . .	9	0.28		
71 to 80 . . . . .	1	0.03		
Total . . . . .	3255	100.00	3669*	100.00

\* From Hamburg statistics for the years 1886-1887.

**Yearly Distribution.** It is interesting to note that we have found the disease prevalent in every year of the period of our study with the exception of the first three years, when, due perhaps to the fact that our people were not yet accustomed to seek institutional care, the number of cases admitted, was smaller. There was no apparent tendency to diminution in any given year. (Table II.)

TABLE II.—YEARLY TYPHOID FEVER ADMISSIONS IN THE PHILIPPINE GENERAL HOSPITAL FROM 1911 TO OCTOBER, 1927, INCLUSIVE.

Year.	Total number of cases.	Year.	Total number of cases.
1911 . . . . .	37	1921 . . . . .	143
1912 . . . . .	74	1922 . . . . .	254
1913 . . . . .	78	1923 . . . . .	260
1914 . . . . .	167	1924 . . . . .	228
1915 . . . . .	89	1925 . . . . .	286
1916 . . . . .	162	1926 . . . . .	292
1917 . . . . .	339	1927 . . . . .	220*
1918 . . . . .	240		
1919 . . . . .	227		
1920 . . . . .	159	Grand total . . . . .	3255

Cases for November and December, 1927 were not included.

TABLE III.—MONTHLY DISTRIBUTION OF TYPHOID FEVER CASES ADMITTED TO THE PHILIPPINE GENERAL HOSPITAL  
FROM JANUARY, 1911, TO OCTOBER, 1927, INCLUSIVE.

Months.	1911.	1912.	1913.	1914.	1915.	1916.	1917.	1918.	1919.	1920.	1921.	1922.	1923.	1924.	1925.	1926.	1927.	Total.
January . .	10	3	8	5	5	4	24	16	21	8	7	23	15	30	26	18	26	239
February . .	2	7	7	9	1	2	36	8	24	2	3	35	23	27	24	27	19	256
March . .	1	5	7	17	11	16	21	15	20	11	11	33	7	16	18	21	20	250
April . .	6	1	2	16	12	19	23	18	20	16	9	11	14	24	28	29	20	268
May . .	5	6	2	16	17	20	29	35	18	21	18	24	25	20	31	27	18	332
June . .	4	4	4	8	6	18	19	21	21	16	11	16	20	20	24	20	22	254
July . .	7	4	7	14	4	19	22	10	21	11	11	21	36	21	28	19	29	284
August . .	5	6	10	23	9	24	54	19	12	18	16	15	30	22	17	40	24	344
September . .	0	8	7	29	4	13	42	27	15	17	11	19	27	13	31	29	23	315
October . .	0	13	5	13	6	9	30	51	20	11	18	26	29	13	24	20	19	307
November . .	4	7	9	10	6	4	26	11	22	12	11	18	18	11	17	18	..	204
December . .	3	10	10	7	8	14	13	9	13	16	17	13	16	11	18	24	..	202
																		3255

NOTE.—Cases for November and December, 1927, were not included.

**Monthly Distribution.** The disease may be said to prevail throughout the entire year. The curve of distribution attains its height during the rainy months with the greatest number of cases occurring in the month of August.

**Complications.** Many and various were the complications of typhoid fever that have been found and their relative frequency of occurrence in different organs of 3255 cases is noted in Table IV.

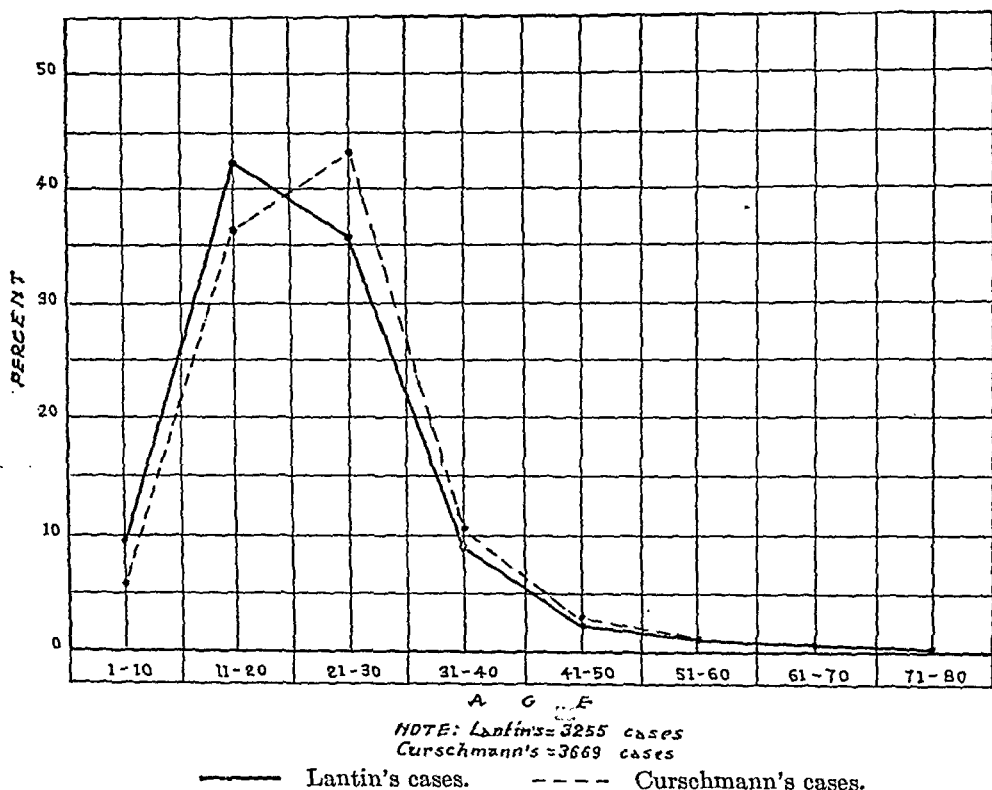


CHART I.—Age distribution of typhoid fever cases admitted to the Philippine General Hospital from January, 1911, to October, 1927, inclusive, compared with Curschmann's data. (See Table II.)

**Peculiarities of Complications.** The complications of typhoid fever require very serious consideration on account of the important rôle they play in the course of the disease. Besides this, they are the deciding factors as to the ultimate outcome of the life of the patient.

There are many disadvantages encountered in properly combating the complications. The difficulty lies mostly in the facts that they are often unpreventable, and that there are neither reliable methods of properly avoiding them nor exact means of knowing when they are near at hand. Even the apparently mildest form of typhoid infection may never be entirely free from the danger of developing serious complications. Mild cases may, therefore, end fatally, due to the unexpected appearance of some serious complications.

TABLE IV.—SHOWING THE RELATIVE FREQUENCY OF OCCURRENCE OF COMPLICATIONS IN DIFFERENT ORGANS IN SO MANY OF 3255 CASES OF TYPHOID FEVER AS FURNISHED DEFINITE RECORDS OF PRESENCE OR ABSENCE OF EACH OF THE INDICATED COMPLICATIONS.

Order.	Complications by organs.	Complication present		Complication absent		Total cases with record.
		Number.	Per cent.	Number.	Per cent.	
1	Pulmonary	441	14.0	2814	86.0	3255
2	Alimentary tract	407	13.0	2848	87.0	"
3	Severe toxemia	322	10.0	2933	90.0	"
4	Cardiovascular	211	7.0	3044	93.0	"
5	Kidney	51	2.0	3204	98.0	"
6	Gall bladder and liver	36	1.0	3219	99.0	"
7	Nervous system	17	0.5	3238	99.5	"
8	Bone (osteoperiostitis 1) (osteomyelitis 1)	2	0.06	3253	99.4	"
9	Genital (orchitis 1; vulvo vaginitis 1)	2	0.06	3253	99.4	"
10	Complications other than above stated	107	3.0	3148	97.0	"

We can better appreciate the importance of typhoid complications when we consider certain peculiarities, inherent with the disease, namely: (1) The long course of illness; (2) the morbid processes progressively taking place in the small bowel; (3) the poisons and their effects on the organs of the body. These factors either alone or combined can produce sooner or later various kinds of complications during the course of the illness. For instance: (1) The long process of illness always predisposes the patient to heart and lung complications; (2) the morbid ulcerative process in the bowels frequently leads to intestinal hemorrhages and perforations; (3) the poisons, depending upon the virulence of the organisms, produce toxic effects principally on the vital organs. These complications *per se* are serious. The dictum that the patient does not die without the complications is particularly true in typhoid infections. In fact, in the present study the unusual high fatality rate is due to the different complications, all serious in nature.

**Frequency of Occurrence of Different Complications.** 1. *Intestinal Hemorrhage.* In Table V, where the absolute relative frequency of occurrence of the different complications is shown, intestinal hemorrhage comes out foremost.

1. *Intestinal Hemorrhage.* Out of 3255 cases of typhoid fever, there occurred 338 cases of intestinal hemorrhage (10.3 per cent). The morbid process in the intestinal tract resulting in hemorrhage is well known to all and because of the usual ulcerative process in the intestines, it is very difficult to foretell whether we can avoid hemorrhage or can always control it. Hence the seriousness of this complication. The hemorrhage may appear without any warning. As a rule, there is no difficulty in the diagnosis of intestinal hemorrhage except in cases in which there is no passage of blood externally.

According to Rolleston<sup>6</sup> this complication was observed in 9.1 per cent of the cases treated in the Metropolitan Asylums Board Hospitals in England.

TABLE V.—SHOWING THE ABSOLUTE RELATIVE FREQUENCY OF OCCURRENCE OF DIFFERENT COMPLICATIONS IN SO MANY OF 3255 CASES OF TYPHOID FEVER AS FURNISHED DEFINITE RECORDS OF PRESENCE OR ABSENCE OF EACH OF THE INDICATED COMPLICATIONS.

Order.	Complications.	Complication present		Complication absent		Total cases studied.
		Number.	Per cent.	Number.	Per cent.	
1	Intestinal hemorrhage	338	10.3	2917	89.7	3255
2	Severe toxemia	322	9.89	2933	90.11	"
3	Acute myocarditis	220	6.75	3035	93.25	"
4	Lobar pneumonia	145	4.45	3110	95.55	"
5	Bronchopneumonia	133	4.08	3122	95.92	"
6	Pulmonary congestion	81	2.48	3174	97.52	"
7	Acute bronchitis*	66	2.02	3189	97.98	"
8	Asthenia typhoid	43	1.32	3212	98.68	"
9	Acute nephritis	39	1.19	3216	98.81	"
10	Intestinal perforation	38	1.16	3217	98.84	"
11	Acute cholecystitis†	34	1.04	3221	98.96	"
12	Peripheral neuritis	16	0.49	3239	99.51	"
13	Severe anemia not due to hemorrhage	15	0.46	3240	99.54	"
14	Parotitis	15	0.46	3240	99.54	"
15	Otitis media	9	0.27	3246	99.73	"
16	Acute fibrinous pleuritis	7‡	0.21	3248	99.79	"
17	Multiple abscesses, kidney	6	0.18	3249	99.82	"
18	Acute appendicitis	6	0.18	3249	99.82	"
19	Ulcer decubitus	5	0.15	3250	99.85	"
20	Furunculosis	5	0.15	3250	99.85	"
21	Acute conjunctivitis	4	0.12	3251	99.88	"
22	Pyonephrosis	3	0.09	3252	99.91	"
23	Acute tonsillitis	3	0.09	3252	99.91	"
24	Pyelitis	3	0.09	3252	99.91	"
25	Bleb formations	2	0.06	3253	99.94	"
26	Hemorrhage, gums	2	0.06	3252	99.94	"
27	Acute endocarditis	2	0.06	3253	99.94	"
28	Thrombophlebitis	2	0.06	3253	99.94	"
29	Pharyngitis	2	0.06	3253	99.94	"
30	Pleurisy with effusion	2	0.06	3253	99.94	"
31	Inguinal adenitis nonsuppurative	2	0.06	3253	99.94	"
32	Corneal ulcer	2	0.06	3253	99.94	"
33	Gangrene, skin face and lips	2	0.06	3253	99.94	"
34	Noma	1	0.03	3254	99.97	"
35	Pericardial effusion	1	0.03	3254	99.97	"
36	Phlebitis, forearm	1	0.03	3254	99.97	"
37	Pulmonary atelectasis	1	0.03	3254	99.97	"
38	Pulmonary gangrene	1	0.03	3254	99.97	"
39	Pleuropericarditis	1	0.03	3254	99.97	"
40	Hemorrhage, lung	1	0.03	3254	99.97	"
41	Multiple liver abscess	1	0.03	3254	99.97	"
42	Acute hepatitis	1	0.03	3254	99.97	"
43	Osteoperiostitis	1	0.03	3254	99.97	"
44	Osteomyelitis	1	0.03	3254	99.97	"
45	Orchitis	1	0.03	3254	99.97	"
46	Vulvovaginitis	1	0.03	3254	99.97	"
47	Axillary adenitis	1	0.03	3254	99.97	"
48	Abscess, legs	1	0.03	3254	99.97	"
49	Typhoid spine	1	0.03	3254	99.97	"
50	Other than that above§	13	0.39	3242	99.61	"

\* 3 cases suppurative

† 2 cases suppurative and perforated.

‡ All these 7 cases were found in autopsy.

§ Abortion 12 cases; threatened abortion, 1 case.

2. *Severe Toxemia*. Severe toxemia comes second in frequency in our series. Only the severe form is included in this series because in a given case this type has considerable clinical importance. This complication depends mainly upon the virulence of the organisms, and the natural resistance of the patient. Thus, the severity of toxemia varies in different individuals, and in different epidemics. We observed 322 severe cases (9.9 per cent).

Toxemia is unavoidable in typhoid infection. There is bacteriemia and in view of the continuous supply of poisons produced by the infecting organisms, strictly speaking, every case of typhoid fever must inevitably have toxemia. In the present series, as was previously stated, only the severe type is included because it has more clinical value. The typhoid toxins are poisonous to the vital organs of the body and in the long run must have telling effects upon them. The central nervous and the cardiovascular systems frequently manifest toxic effects. When these are affected very severely, the condition becomes almost always hopeless. The symptoms of toxemia are manifested in various ways depending upon the organs mostly affected. In cases where the central nervous system is chiefly affected, symptoms and signs referable to that system are the more prominent; and where the heart is mainly involved, symptoms and signs referable to this particular organ are the more markedly noted. When the nervous and cardiovascular systems are both affected, combined symptoms referable to these organs will be manifested.

3. *Acute Myocarditis*. The third complication in frequency is acute myocarditis. We observed it in 220 cases (6.75 per cent). This high number should not cause surprise. We believe that there should be more than 220 cases of myocarditis, because in infectious diseases, particularly typhoid fever, which generally has a long course and in which the organisms continuously elaborate toxins, the vital organs, like the heart, do more frequently yield to their effect. The heart cannot withstand the continuous and prolonged intoxication without showing signs of myocardial weakening. This is not merely a theoretical consideration; on the contrary the cases that were autopsied showed distinct myocardial degenerative lesions. Rolleston states:<sup>6</sup>

"While endocarditis and pericarditis are very uncommon in typhoid fever and rarely detected until the autopsy, myocarditis is very frequent, being said to occur clinically in four-fifths of all cases.

"Unless, however, a careful watch has been kept over the heart, this complication is very liable to escape detection, and the first indication of its presence may be a sudden fatal syncopal attack.

"The principal signs of myocarditis are weakness of the first sound, first at the apex and then at the base, a change in the character of the cardiac rhythm, as shown by tachycardia, embryo-

cardia, gallop rhythm, or much less frequently bradycardia, the development of a murmur, and a low blood pressure (Widal, Lemierre and Abrami).

"Though most likely to occur in a severe attack, myocarditis, may be found even in mild cases. The date of its occurrence is rarely before the second or third week."

If, however, the toxic lesions are central, specially affecting the bulbar region, where important centers are found, the diagnosis of myocarditis becomes then very difficult. In these instances, the cases may show low blood pressure and disturbed cardiac rhythms.

4. *Lobar Pneumonia*. The fourth in frequency of complications noted in our series is lobar pneumonia. There were observed 145 cases (4.5 per cent). The severity of the infection, and the prolonged recumbent position naturally predispose the patient to lung complications. Many of the cases showed unresolved pneumonia and this particular condition was specially noted in the many fatal cases that were autopsied in which typhoid ulcers were found already healed.

5. *Bronchopneumonia*. This was observed in 133 cases (4 per cent). The factors favoring this particular complication are the same as those of lobar pneumonia.

6. *Pulmonary Congestion*. This condition is usually observed at about the end of the second week. This complication is the result of prolonged recumbent position, although a myocardial weakness and other morbid conditions may contribute. In our series, pulmonary congestion constitutes 2.08 per cent of the total.

7. *Acute Bronchitis*. Here are included only those cases with severe respiratory symptoms. The danger in these is that they may become suppurative. This condition did really occur in three of our cases. They may lead to pneumonia or bronchopneumonia. Furthermore, severe bronchitis will throw extra load to the heart.

8. *Typhoid Asthenia*. This is a very serious complication. The patients usually die except in exceedingly rare instances. In our series only one recovered out of 43 cases; 4 cases were discharged unimproved and the remaining 38 cases died. The exact pathologic lesions responsible for this complication are not definitely known, although some French writers, specially Sergent (as cited by Rolleston<sup>6</sup>) believe that the lesions are in the suprarenals, so much so that the condition was always referred to by them as suprarenalitis. The symptoms most commonly observed in our series are marked general weakness, prostration, gradual but progressive emaciation accompanied by small rapid pulse, loss of appetite, at times nausea, vomiting, and moaning. There is tendency for the temperature to become irregular, and finally to be subnormal. This complication was observed in 1.3 per cent of our cases.



In Table VI, the frequency of the complications among our cases is compared with those observed by other authors. The percentage of intestinal hemorrhage in our cases is almost identical with that of Rolleston,<sup>6</sup> but higher than that of Curschmann.<sup>2</sup> Pulmonary complications are more frequent in ours than those of Rolleston. They (Curschmann and Rolleston) had more cases of intestinal perforations. In other cases, our observations were almost identical with theirs. It may be said, therefore, that except in a few instances noted above, our findings do not differ much from those of other authors working in other climates.

TABLE VI.—FREQUENCY OF COMPLICATIONS IN TYPHOID FEVER OBSERVED BY DIFFERENT AUTHORS.

Complications.	Our cases.	Rolleston.	Curschmann.
	Per cent.	Per cent.	Per cent.
Intestinal hemorrhage .	10.3	9.13	4 to 6
Lobar pneumonia . .	4.45	2.52	No figure
Bronchopneumonia . .	4.08	1.11	No figure
Intestinal perforation .	1.16	3.41	3
Peripheral neuritis . .	0.49	0.30	No figure
Parotitis . . . . .	0.46	0.65	0.30 to 0.50
Pleurisy . . . . .	0.24	1.11	No figure
Bed sores . . . . .	0.15	No figure	1 to 1.90
Periostitis . . . . .	0.03	1.6	No figure

**Fatality.** Out of 3255 cases of typhoid fever admitted to the Philippine General Hospital from January, 1911, to October, 1927, inclusive, 629 died (19.2 per cent).

With regard to typhoid fatality Widal, Lemierre and Abrami<sup>7</sup> emphasize the variability of results obtained.

"Griesinger placed the mortality rate at 20 per cent; Murchison, at 15.82 per cent and Jaccoud working on a total of over 64,600 cases, gathered from various statistics, gave a mortality of 19.64 per cent."

They found that hospital mortality is always higher on account of the surrounding, because of late admissions and also because of epidemic complications which often supervene in hospital cases (diphtheria, etc.).

"The English statistics studied by Murchison for a period of thirty-three years give the mortality rate of 15.8 per cent. The French statistics give very variable results, according to the season and place. Chomel in Paris gave 22 per cent; Glenard of Lyon, 9 per cent. The statistics in Paris from 1866-1894 varied from 14 to 24 per cent."

Our findings showed that deaths in typhoid fever were invariably due to complications. The principal complications that caused deaths may be classified in general as follows: (1) Intestinal, both hemorrhage and perforations; (2) cardiac; (3) pulmonary; (4) severe toxemia; (5) severe anemia not due to hemorrhage; (6)

asthenia; (7) parotitis; (8) nephritis, and a few others as shown in Table VII.

TABLE VII.—CASES OF TYPHOID FEVER WITH CERTAIN NOTED COMPLICATIONS TERMINATING FATALLY.

Complications.	Cases.	Deaths.	Fatality rate, per cent.
Acute hepatitis . . . . .	1	1	100.00
Pulmonary gangrene . . . . .	1	1	100.00
Hemorrhage, lungs . . . . .	1	1	100.00
Pulmonary atelectasis . . . . .	1	1	100.00
Multiple liver abscess . . . . .	1	1	100.00
Suppurative cholecystitis perforated . . . . .	2	2	100.00
Pulmonary abscess . . . . .	3	3	100.00
Multiple abscesses kidney . . . . .	6	6	100.00
Intestinal perforation* . . . . .	38†	37	97.36
Asthenia . . . . .	43‡	39	90.70
Acute myocarditis . . . . .	220	160	72.73
Severe toxemia . . . . .	322	191	59.32
Bronchopneumonia . . . . .	133	77	57.89
Lobar pneumonia . . . . .	145	80	55.17
Severe anemia not due to hemorrhage . . . . .	15	8	53.33
Intestinal hemorrhage . . . . .	338	134	39.64
Parotitis . . . . .	15	5	33.33
Acute nephritis . . . . .	39	9	23.08

\* Most of the cases verified by autopsy.

† One case discharged unimproved against advice.

‡ One case recovered, and 4 cases discharged unimproved.

Table VII shows the very many complications that cause an unusually high fatality rate. Many deaths were to be expected due to the seriousness of the complications, namely, intestinal perforations, perforating cholecystitis, pulmonary gangrene and abscess, asthenia, repeated and profuse intestinal hemorrhage, severe myocarditis, severe toxemia, and so forth. Our fatality rate of 39.6 per cent for intestinal hemorrhage is very high. Curschmann<sup>2</sup> gives only 20 to 30 per cent average fatality rate for this complication and 40 per cent as the maximum limit.

The fatality in our cases with pulmonary complications, particularly the pneumonias, is high. The principal factors responsible for this may be stated as follows: (1) Weakened conditions of the patients; (2) presence of myocarditis; (3) the fact that many cases of pneumonia would not undergo resolution, and such unresolved pneumonias were oftentimes noted in the autopsy where the typhoid ulcers were already healed and yet the lungs showed active morbid processes.

It may be noted in Table VII that the deaths recorded exceed the total 626 cases that died. The reason for this is the fact that, in many instances, a single death had several anatomic diagnoses. It becomes, therefore, very difficult to state with certainty which particular kind of complication the patient died of. For instance, a case with severe toxemia died with anatomic diagnosis of myocarditis, lobar pneumonia, and so forth. In this particular instance,

we believe that death would be due to the combined effects of the primary disease and the complications present.

Of the cases of typhoid fever that terminated in death there were 410 males and 216 females, constituting 20 per cent and 17.9 per cent sex fatality respectively. The great majority of deaths occurred in the age groups eleven to thirty years where 535 deaths occurred (85.4 per cent of the total 626 deaths). At Hamburg, Curschmann<sup>2</sup> stated that the fatality among men was 8.5 per cent, as against 3.5 per cent among women in 1886. In 1887, the fatality was 8.8 per cent among men, and 9.4 per cent among women. Murchison<sup>2</sup>

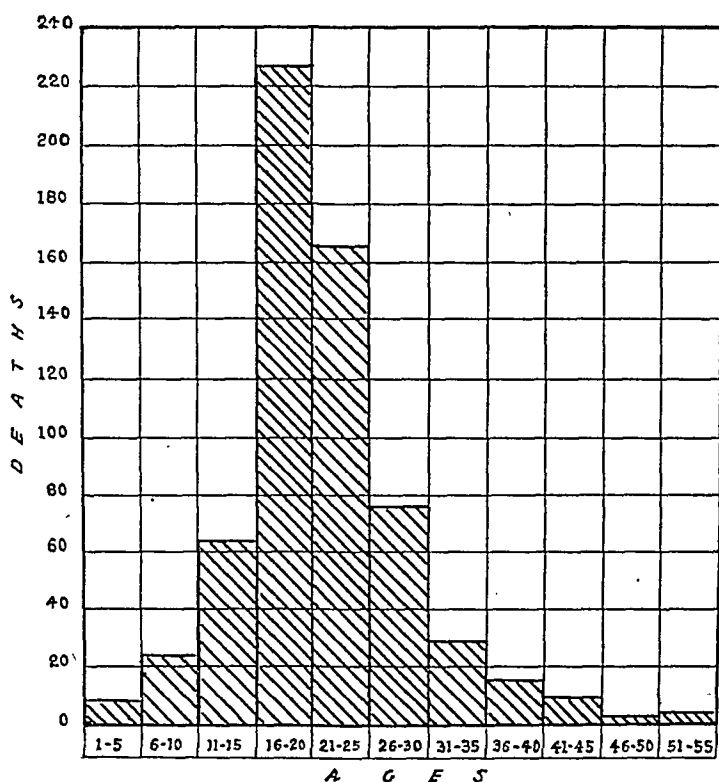


CHART II.—Age distribution of typhoid fever deaths in the Philippine General Hospital from January, 1911, to October, 1927, inclusive.

between the years 1848 and 1857 found the fatality in 1820 cases of the disease treated in the London Fever Hospital to be as follows: 17.7 per cent in males, and 18.9 per cent in females.

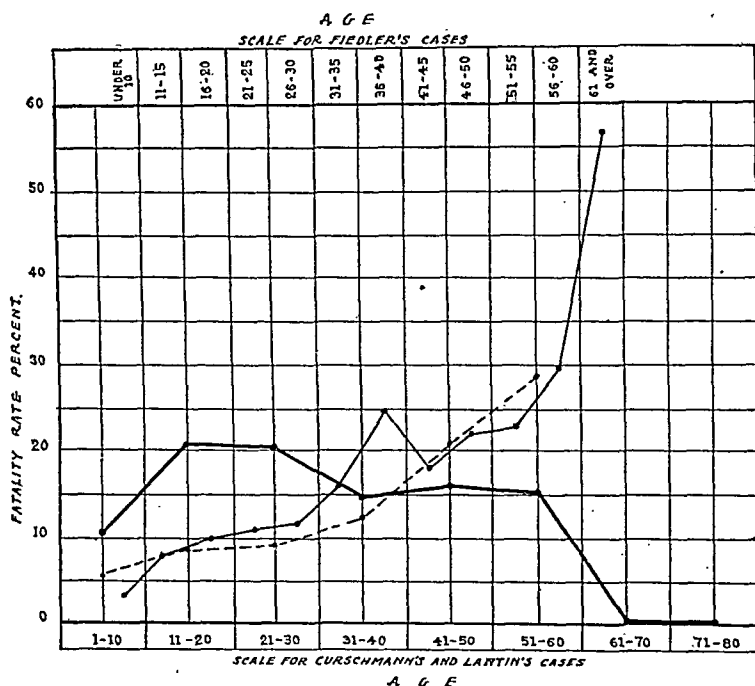
Graph II shows the age distribution of deaths by five year age groups. After the age of fifty-five years, there was no mortality observed.

We observe in our cases that the disease is more fatal in the second and third decades of life. After the third decade, the fatality rate decreases and the disease is apparently benign in the sixth and seventh decades of life among Filipinos.

This observation seems to differ from that of McCrae<sup>5</sup> working in temperate climates. He says:

"Up to the age of two years the risk is great; from two to fifteen years is the most favorable period and the mortality is low. As a rule from about fifteen up to twenty-five is a more favorable period than from twenty-five to forty years. After forty, the danger increases with every year and over the age of fifty the death rate is high."

Comparing our fatality rate with that of Curschmann<sup>2</sup> it will be noted that generally speaking the fatality among Filipinos from the first decade to the third is high, about twice as much as that observed by Curschmann in Europe. After the third decade, the fatality in our cases begins to decrease while that of Curschmann's went up. Graph III is compared with Fiedler's curve.<sup>3</sup> This author studied the cases of the Dresden City Hospital during thirty-four years (1850-1883).



Note: Lantin's = 3255 cases. Curschmann's = 3669 cases.

— Lantin's. - - - Curschmann's. — Fiedler's.  
Fiedler's data: Result of thirty-four years' experience.

CHART III.—Fatality rate of typhoid fever cases admitted to the Philippine General Hospital from January, 1911, to October, 1927, inclusive, by ages (our cases compared with those of Curschmann).

We can say in general that the European statistics tend to show that the fatality rate increases as the age advances. This is in marked contrast to that observed among Filipinos where after the third decade, the fatality rate decreases gradually until the sixth decade, when the disease seems to appear benign, none of our cases which occurred above the age of fifty-five having died.

**Yearly Fatality.** The yearly fatality rate of typhoid fever cases showed a wide variation. The range is from 7 to 28.1 per cent

while the percentage given by Murchison<sup>6</sup> is 12.82 to 28.42 per cent; by McCrae,<sup>4</sup> 7 to 20 per cent; and by Anders,<sup>1</sup> 8 to 10 per cent.

The factors influencing the variation of fatality from year to year are several, namely: (1) The virulence of the organisms; (2) the resistance of the individuals; (3) the presence and nature of the complications; and (4) the presence or absence of some other kinds of epidemic prevailing in the season; (5) the duration of illness

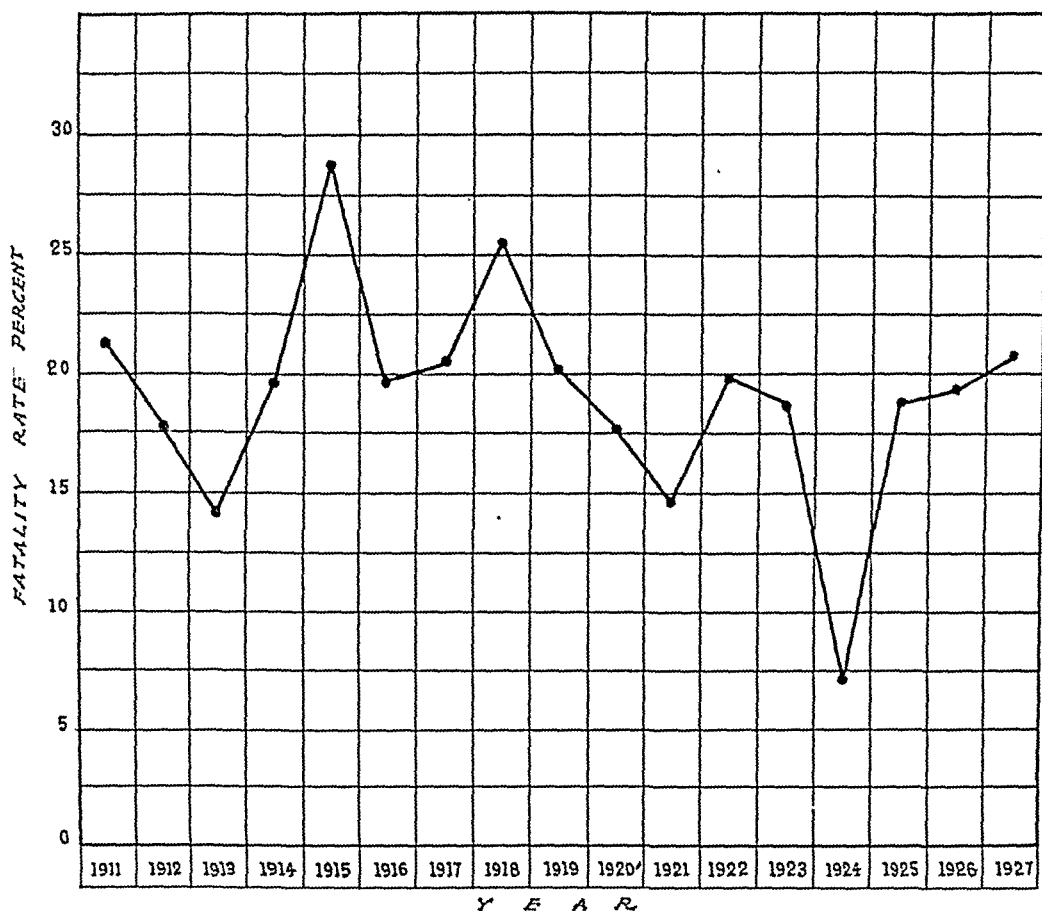


CHART IV.—Case fatality rate of typhoid cases admitted to the Philippine General Hospital from January, 1911, to October, 1927, inclusive.

before treatment was begun; and (6) the influence of typhoid vaccine, employed as preventive measure.

These factors are too well known to require much discussion. It is generally accepted that the greater the virulence of the organisms, the higher the fatality rate becomes, and this is true in typhoid infection. The higher the resistance of the patient the lower must the fatality rate be. It is very peculiar, indeed, to observe in typhoid infections that the strong, the robust and the young adults frequently succumb, while a significant proportion of those weaker in constitution survive.

The presence and nature of complications as well as the prevailing state of health in the community greatly affected the fatality rate. The presence of other epidemics like the pandemic of influenza in 1918 and 1919 really influenced a good deal the fatality rate of the disease during those periods due to frequent lung complications. In 1918, the fatality rate was 25.8 per cent and in 1919, 20 per cent.

The duration of illness when the treatment begins will affect to a great extent the fatality rate. From our experience, we noted that the great majority of our typhoid cases were laborers who did not realize the advantage of early hospital treatment, and remained, as a rule, too long without medical attention in their homes, where the hygienic conditions were very poor. An even worse factor was that they used to go to bed only when they became too weak to work. As a rule, these cases are admitted to the Philippine General Hospital under these unfavorable conditions, already in the advanced stage of the disease, many of them with serious complications.

The good results obtained by the widespread use of typhoid vaccine as a prophylactic measure are well known to all, as shown in the reduced typhoid fatality in the armies since the introduction of typhoid vaccination.

Graph IV shows the yearly fatality rate of typhoid fever cases from January, 1911, to October, 1927, inclusive. The average fatality rate in our series of 3255 cases is 19.2 per cent which compares favorably with various statistics observed in the temperate climates.

**Conclusions.** 1. The deaths in typhoid fever are due to grave complications.

2. In the frequency of occurrence of complications in different organs of 3255 cases of typhoid fever from January, 1911, to October, 1927, inclusive, the pulmonary complications head the list, constituting 14 per cent; alimentary tract, 13 per cent; severe toxemia, 10 per cent; cardiovascular, 7 per cent; kidney, 2 per cent; gall bladder, liver, 1 per cent; nervous system, 0.5 per cent; bone (osteoperiostitis 1, osteomyelitis 1) 0.06 per cent; genital (orchitis 1, vulvovaginitis 1) 0.06 per cent; and other complications, 3 per cent.

3. In the occurrence of particular complications, the intestinal hemorrhage was the most frequent, constituting 10.3 per cent; severe toxemia, 9.9 per cent; acute myocarditis, 6.7 per cent; lobar pneumonia, 4.4 per cent; bronchopneumonia, 4.1 per cent; pulmonary congestion, 2.5 per cent; acute bronchitis, 2 per cent; asthenia, 1.3 per cent; acute nephritis, 1.2 per cent; intestinal perforation, 1.2 per cent; acute cholecystitis, 1.0 per cent. All other complications were less than 1 per cent apiece.

4. Our fatality rate from the first decade to the third, is generally high, about twice as much as the figures obtained by Curschmann.

After this decade (third), it decreases until the sixth. The statistics in the temperate climates clearly show that the fatality rate increases as the age advances, in marked contrast with our observations among Filipinos that after the third decade the fatality rate decreases until the age of fifty-five years when the disease showed no mortality.

5. Out of 3255 cases, 2547 (78.25 per cent) occurred between the ages eleven to thirty years.

6. The great majority of deaths occurred in the age groups from eleven to thirty years, (535 cases representing 85.4 per cent of the total 626 that died).

7. The average fatality rate in our series, covering a period of sixteen years and ten months, is 19.2 per cent. This compares favorably with various statistics observed in the temperate climates.

8. There is considerable yearly variation in the fatality rate of this disease (7 to 28.1 per cent).

9. From our experience we noted that more frequently the robust, the strong and the young adults succumb to typhoid infections, in contrast with the more frequent survival of those that are less strong in constitution.

NOTE.—The authors are grateful to Prof. José Albert, Chief of the Department of Pediatrics for permitting us to include the cases in pediatrics in our study; to Professors Ariston Bautista, Luis Guerrero, Hilario Lara, Walfrido de Leon and Juan C. Nafias for valuable suggestions; and to our associates, Doctors A. Pedroche, J. Linan, J. Hizon, and A. Gutierrez, for their coöperation.

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## THE EFFECT OF GASTROINTESTINAL OPERATIONS ON THE EMPTYING OF THE GALL BLADDER.\*

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AFTER an abdominal operation has been completed in an attempt to reestablish normal physiologic relations, one may be left with the disquieting thought that organs adjacent to, or affected by those

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incised may no longer function normally; nor is it reasonable to suppose that an integral part of a mechanism should be unaffected by the manipulation of another part. One might be justified in believing that some change from normal might result. It is known that certain changes occur in the stomach from disturbances of physiologic relations, alterations in acidity, motility, and size often making this only too apparent. One might believe, therefore, that these changes affect the normal function of the gall bladder because of its proximity, and also because it is definitely known that biliary flow is affected by changes in the activity of the gastrointestinal tract. Thus, for example, excision of the gall bladder causes extrahepatic biliary dilatation,<sup>1 6 8 9 13 14 15 20 23</sup> and destruction of the ampulla of Vater produces changes in biliary flow.<sup>15</sup>

It has been shown that the normal gall bladder empties its contents intermittently. Its several functions, of which I shall speak later, are evidently related to the ingestion and metabolism of foodstuffs, especially fats.<sup>4 5 7 10 11 19 22 24 25 26 27</sup> There is a great deal more to be learned about the gall bladder and in the future it will probably seem far more important to know the exact mechanism of correlation with the adjacent organs than present knowledge implies. It is, however, important for the surgeon to know just how the normal mechanism is affected by the operation, even though his knowledge of the important functions of the organ is still incomplete.

It was my purpose in this research to determine the effect of various types of gastrointestinal operation on the normal emptying of the gall bladder. The study is based primarily on the work of Boyden,<sup>3 4 5</sup> Higgins and Mann,<sup>10 11</sup> Hamrick and Whitaker<sup>19 22 24 25 27</sup> who have shown both independently and in collaboration<sup>26</sup> that the gall bladder in man and in animals empties its contents following a meal of egg yolk and cream. Whereas protein causes some degree of emptying and fats a considerable degree, the maximal degree of emptying is caused by a meal of egg yolk and cream. Consequently, we have an excellent index of the normal activity of the gall bladder in the effect of such a specific activator, and if alterations in the gall bladder were caused by some change in the adjacent gastrointestinal tract they should be reflected in this process of emptying.

Sosman<sup>22</sup> has shown that the gall bladder of a patient on whom pylorotomy and gastrojejunostomy had been performed emptied normally. Whitaker<sup>25</sup> performed the same operations on three dogs with no effect on the gall bladder.

Just how this emptying process proceeds, whether it is active or passive, what excites it and through what mechanism or system the stimulation comes, are subjects of many interesting observations.

A review of the theory and experimental work on factors believed to influence or cause emptying of the gall bladder shows that they comprise four important groups: (1) extrinsic; (2) intrinsic; (3) reflex, and (4) hormonal. Extrinsic factors are such possible aids to the



emptying as respiration, changes in intraabdominal pressure, and duodenal peristalsis. Intrinsic factors are contractility or elasticity of the gall bladder, causing emptying. This brings up the question of whether or not the gall bladder empties because of its intrinsic mechanism. Opinion now favors this belief. Reflex factors include the direct nervous reflexes by the splanchnics and the vagi, and also the indirect nervous reflexes through indefinite paths by means of reciprocal innervation between the gall bladder and the sphincter of Oddi. Hormonal factors include acid chyme, hydrogen-ion concentration, secretin, and food products such as peptone or oils that by their presence exert a humoral specific influence on the emptying or some similar mechanism and especially the new hormone discovered by Ivy and Oldberg.

The significance of the gall bladder as an organ is better understood if not only its relation to disease is considered, but also the functions ascribed to it. Besides its proved function of emptying its content of bile, it has been definitely shown to concentrate the bile entering it from seven to ten times.<sup>21</sup> The gall bladder is considered to act as a regulator<sup>16 17</sup> of bile flow and pressure. It stimulates the liver to increased activity at the time when the gastrointestinal tract is most active.<sup>18</sup> The suggestion has been made that the gall bladder by some influence, perhaps by means of a hormone, regulates gastrointestinal motility<sup>2</sup>; therefore, the determination of the ways in which gastrointestinal operations may affect the normal emptying of the gall bladder assume greater importance.

**Method.** Dogs were used in these experiments and a general plan of procedure was adhered to, in order to establish a certain group of standards. To produce a uniform condition the animal was fasted for twenty-four hours. Four hours before exploratory operation under general anesthesia, the animal was fed from 350 to 450 cc. of a mixture of egg yolk and cream, the amount depending on the size and the appetite of the animal. Exploration was performed at the end of the four hours. The gall bladder was carefully exposed and examined and the degree of emptiness determined. At the same time, the lacteals were inspected to determine the extent of ingestion and absorption of the meal of egg yolk and cream. After recovery, various types of gastrointestinal operations were performed on the animals. Following varying intervals (from three weeks to more than a month) the animals were again fed the fat meal, the abdomen was opened under general anesthesia and the degree of emptiness of the gall bladder noted. This observation was repeated in many cases.

A year or more after operation, a group of animals was given the fat meal and exploration performed. In all 38 animals were used in these experiments. It was thought that by using a series of this size and by checking the results after such a length of time the percentage of error would be minimized.

**Results.** The results are expressed in terms of the degree of gall bladder contraction, which may be said to be marked, moderate, slight, or absent. These terms are only relatively exact, but nevertheless are as exact as is necessary to express the ability of the organ to empty. Inasmuch as even in a series of normal animals, used as controls, variation in the degree of contraction of the gall bladder was noted, the difficulty of determining the exact relative degree of emptiness of the organ is obvious. If the gall bladder was finally found markedly contracted, or more contracted than at a previous observation, it was thought justifiable that the more positive result should replace the former less positive result, and the final result was tabulated.

Three series of experiments have been grouped. In the first group, 8 animals were used as controls. In the second series, various types of gastrointestinal operations have been performed to determine the effect on the emptying of the gall bladder. There were 34 animals in this group and many different types of operations were performed. In the last group, reexploration was performed in 10 cases after a year had elapsed.

A survey of Tables I, II, III and IV shows rather conclusively that the emptying of the gall bladder is not influenced by various types of gastrointestinal operations. If in Table III the percentages of marked and moderate contraction are added, it is seen that in the control group there is a total of 87 per cent, while in the experimental group (Table II) there is a total of 88 per cent. Within certain unavoidable limits of error, marked or moderate contraction must be considered normal in gall bladders of this series four hours after the feeding of egg yolk and cream. This conclusion is obvious in a comparison of the results in the control and in the experimental groups (Table III).

TABLE I.—EFFECT OF FAT MEAL ON GALL BLADDERS OF NORMAL ANIMALS.

	Cases.	Per cent.
Marked contraction . . . . .	4	50.0
Moderate contraction . . . . .	3	37.5
Slight contraction . . . . .	1	12.5
Total . . . . .	8	100.0

**Discussion.** It may be stated definitely that there is no change in the normal function of emptying even after as long as a year. If any conclusions regarding the change in the process of emptying are to be drawn from the observations in 10 cases a year after operation (Table IV), they might indicate improvement in the process rather than the reverse. However, the only allowable conclusion is that there is no change from normal even after a year. It should be stated that in this series there were 4 cases in which the initial observation was made before gastrointestinal operation was per-

formed, and postoperative observations were not made until a year later. The other 6 cases were observed after operation on two occasions a year apart.

TABLE II.—REACTION OF GALL BLADDER IN CASES IN WHICH VARIOUS TYPES OF GASTROINTESTINAL OPERATION HAD BEEN PERFORMED.

Types of operation.	Cases.	Marked contraction.	Moderate contraction.	Slight contraction.	No contraction.
Polya resection . . . . .	12	7	4	1	1
Devine operation . . . . .	1				
Anterior gastroenterostomy . . . . .	6	5		1	
Anterior gastroenterostomy with pyloric closure . . . . .	2		1	1	
Rous gastroenterostomy . . . . .	1		1		
Finney pyloroplasty . . . . .	7	5	2		
Judd pyloroplasty . . . . .	1	1			
Horsley pyloroplasty . . . . .	2	1	1		
Jejunal pyloric anastomosis . . . . .	1	1			
Jejunum-ileoduodenal anastomosis . . . . .	1	1			
Total . . . . .	34	21	9	3	1

TABLE III.—COMPARISON OF REACTION OF GALL BLADDERS IN NORMAL ANIMALS AND IN THOSE ON WHICH THERE WAS GASTROINTESTINAL OPERATION.

	Control group.		Experimental group.	
	Cases.	Per cent.	Cases.	Per cent.
Marked contraction . . . . .	4	50.0	21	61.8
Moderate contraction . . . . .	3	37.5	9	26.5
Slight contraction . . . . .	1	12.5	3	8.8
No contraction . . . . .			1	2.9
Total . . . . .	8	100.0	34	100.0

TABLE IV.—DEGREE OF CONTRACTION A YEAR AFTER OPERATION.

Type of operation.	Degree of contraction.	
	Soon after operation.	One year later.
Anterior gastroenterostomy . . . . .	Marked	Marked
Anterior gastroenterostomy . . . . .	Marked*	Moderate
Rous gastroenterostomy . . . . .	Moderate	Marked
Finney pyloroplasty . . . . .	Marked	Marked
Finney pyloroplasty . . . . .	Moderate	Moderate
Finney pyloroplasty . . . . .	Slight*	Marked
Finney pyloroplasty . . . . .	Marked*	Marked
Finney pyloroplasty . . . . .	Marked*	Marked
Judd pyloroplasty . . . . .	Marked	Marked
Horsley pyloroplasty . . . . .	Marked	Slight

\* Before operation.

In almost all the cases observed the lacteals were found to be rather markedly injected. The injection was variable in extent, and in certain cases in which contraction was not marked, the lac-

teals were poorly injected and, as expected, showed but little absorption of the meal. However, definite conclusions cannot be drawn from this observation as the results are too unsettled. If the degree of absorption in the lymphatics and the blood stream could be definitely measured a correct solution for the variation in the degree of contraction might be found. It is merely proposed that the degree of emptying of the gall bladder is influenced by the amount of absorption of the meal of egg yolk and cream, inasmuch as it is certain that this foodstuff contains something which specifically influences the contraction of the gall bladder.

Two animals in this series were being used also in experiments on ulcer and operations of such a nature had been performed that the gastric contents had no way of coming in contact with the ampulla of Vater. In one operation the duodenum was isolated and the jejunum joined end-to-end with the pylorus. In the other, an end of the divided jejunum was joined to the ileum and the distal end of the severed jejunum anastomosed to the proximal end of the duodenum. In both these cases the gall bladder was markedly contracted. This would apparently indicate that the gall bladder emptied by other means than by acid-chyme stimulation to the duodenal mucosa or by acid-chyme stimulation to the sphincter of Oddi. Since there must have been changes in the acid and alkaline balance in the majority of cases after operation on the gastrointestinal tract it would appear that these factors and the hydrogen-ion factor are not necessary for the emptying of the gall bladder.

**Summary.** A series of experiments was carried out on dogs to determine if the standard clinical types of operations carried out on the stomach would affect the emptying of the gall bladder which follows the ingestion of a fat meal. It was found that the gall bladder gave the normal response to the ingestion of a fat meal following various standard gastric operations.

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## A COMPARISON OF ARSPHENAMIN AND CATARRHAL JAUNDICE, WITH SPECIAL REFERENCE TO THE BLOOD PICTURE.

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**Introduction.** Most investigators have conceded that a distinction between arspenamin jaundice and catarrhal (infectious) jaundice, based on the clinical picture, is difficult. Todd<sup>1</sup> compared 24 cases of arspenamin jaundice with 15 cases of catarrhal jaundice without demonstrating any marked differences, except for the more frequent occurrence of gastrointestinal symptoms in the latter and of

abdominal and liver tenderness in the former. Michie,<sup>2</sup> in a study of 100 patients with jaundice among American troops in Germany, 35 of whom had been treated with arspnenamin, found similar differences. Likewise, Golay,<sup>3</sup> admitting the similarity of these two conditions, offers the following observations concerning arspnenamin jaundice as aids in their differentiation: (1) a history of previous arsenical treatment; (2) the infrequency of temperature reaction; (3) the rarity of complete discoloration of the stools; (4) a firm liver; (5) almost constant urobilinuria; (6) the absence, in most cases, of bradycardia and itching. On the other hand, Ruge<sup>4</sup> reviewing 800 cases of catarrhal jaundice and 333 cases of arspnenamin jaundice, failed to find any important differences between the two conditions. Because of this similarity and certain epidemiologic considerations, he regards arspnenamin jaundice as identical with catarrhal jaundice, modified only by the presence of arspnenamin and syphilis. This view is held by several other authors.

Very little effort, however, has been made to distinguish the two conditions on the basis of their blood pictures. In the case of catarrhal jaundice, this phase has been studied by Jones and Minot<sup>5</sup> and Thewlis and Middleton,<sup>6</sup> who showed that at the height of the jaundice there exists a leukopenia with a relative lymphocytosis. This suggested that observations of the white blood-cell picture of patients with arspnenamin jaundice might aid to determine whether or not it would be of value in diagnosis. This has been done by a study of the records of cases of arspnenamin jaundice.

**Methods and Material.** An analysis has been made of the clinical and laboratory records of 61 cases\* of jaundice; 60 occurring after arspnenamin therapy and one after injections of sodium cacodylate. The patients, representing cases of all stages of syphilis, had received varying quantities of arspnenamin or allied arsenical preparations. Forty of the patients were males and 21, females, varying in age from eighteen to sixty-six years. The cases represent a consecutive series taken from the records of the Massachusetts General Hospital for the years 1914 to 1927 inclusive, with four exceptions. The four cases were excluded for the following reasons: one was complicated by acute nephritis, one could not be differentiated from cholecystitis with cholelithiasis and the other two, both fatal, were probably cases of acute yellow atrophy, possibly due to the arspnenamin.

Records of the white blood-cell counts were available in only 50 of the 61 cases studied and the differential counts in 46 cases. The blood counts utilized in this study were made by many different house physicians. The differential white blood-cell counts were made usually from only 100 cells, which of course leads to noticeable

\* None of the cases could be classified under an Herxheimer reaction.

error, but not to sufficient error to detract from the conclusions based on these counts.

**Symptoms.** In the patients, jaundice appeared at variable periods of time after the last arsphenamin injection, as is shown in Table I. The cases were classified as "early" and "late," the former including those cases in which jaundice occurred in less than two weeks, and the latter, cases in which jaundice developed in two weeks or more after the last dose of arsphenamin. Jaundice appeared on the average eight days after the onset of symptoms, but in the "early" cases it developed in about six and a half days and in the "late" cases in about ten and a half days after symptoms were first apparent.

The literature offers conflicting descriptions of the clinical picture of arsphenamin jaundice. The present series of cases emphasizes the mildness of the disease. Prodromal symptoms were absent in about one-fourth of the cases. When prodromal symptoms were present, they usually consisted of slight malaise, anorexia and nausea, occasional vomiting, mild abdominal distress and transitory muscle and joint pains. Belching and constipation were less common; diarrhea was rare. Only 5 cases showed severe prodromal symptoms which consisted mainly of chills, fever and general weakness.

The symptomatology after the onset of jaundice remained essentially the same as during the prodromal stage. In some instances, however, the appearance of jaundice was attended either by the subsidence of the prodromal symptoms or the beginning of symptoms. In addition to the gastrointestinal disturbances, slight transitory fever and malaise were not uncommon after jaundice appeared. In only two cases did the temperature reach between 102° and 103° F. for a few days. This fact agrees with the observations of Stokes, Ruedemann and Lemon,<sup>7</sup> Scott and Pearson,<sup>8</sup> and Rehder and Beckmann.<sup>9</sup> Itching, headache and generalized weakness occurred sporadically. About half of the patients noticed the urine became dark, some, even before the onset of jaundice. Less than a third noticed light or clay-colored stools.

TABLE I.—TIME OF ONSET OF JAUNDICE AFTER LAST ARSPHENAMIN INJECTION.

	Early cases (26).				Late cases (35).				
	0 to 1 day.	2 to 4 days.	5 to 7 days.	8 to 12 days.	2 to 3 wks.	4 to 8 wks.	9 to 12 wks.	13 to 18 wks.	19 wks.
No. of cases . . .	4	5	8	9	7	7	13	6	2

In general, the symptoms were mild, and a given patient presented few complaints. As recorded in Table II, about 45 per

cent of the patients had either no symptoms or only mild ones. This is in accord with similar statistics given by Zimmern.<sup>10</sup> On the other hand, only 7 cases could be classed as severe, although none of these patients were seriously ill.

TABLE II.—THE SEVERITY OF SYMPTOMS IN ARSPHENAMIN JAUNDICE.

	Early cases.		Late cases.		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
No prodromal symptoms . . . . .	6	23.1	8	22.8	14	23.0
No symptoms throughout course . . . . .	2	7.7	3	8.6	5	8.2
Mild cases* . . . . .	8	30.8	19	54.3	27	44.2
Moderately severe cases . . . . .	14	53.8	13	37.1	27	44.2
Severe cases . . . . .	4	15.4	3	8.6	7	11.5
Totals . . . . .	26	100.0	35	100.0	61	99.9

\* Includes cases without symptoms.

**Findings on Physical Examination.** The most constant finding on physical examination was a palpable liver occurring in about two-thirds of the cases; a tender liver was found in a very few. The spleen was felt in only 4 cases. Bradycardia was uncommon. The records show that the urine contained bile in all but a few of the cases and albumin in about half. The urinary sediment, usually slight, showed cells and hyaline and granular casts in about 60 per cent of the cases. In 57 per cent of the cases the stools were clay-colored as noted on examination or as reported by the patient. These physical and laboratory findings agree with the results recorded by some but not all investigators.

It is to be noted that the "early" cases differed somewhat from the "late" cases in their clinical pictures. Gastrointestinal disturbances and fever were more common in the "early" cases, while abdominal tenderness, an enlarged tender liver and an enlarged spleen were more common in the "late" cases. In general, the "late" cases tended to be milder than the "early."

The usual clinical picture of catarrhal jaundice as described by Jones and Minot,<sup>5</sup> Willcox,<sup>11</sup> Troisier,<sup>12</sup> Williams<sup>13</sup> and others appears to be in definite contrast to the usual clinical picture of arspenamin jaundice, in spite of the fact that some authorities do not consider that differences exist. The feature of these two conditions are contrasted in Table III. In general, the severity as well as the number of symptoms presented by the average case is much greater in catarrhal than in arspenamin jaundice. The physical findings also are somewhat different in the two conditions. Most authorities, for example Rolleston<sup>14</sup> and Blumer,<sup>15</sup> agree that a large and tender liver is common in catarrhal jaundice and a palpable spleen



is not uncommon. This is in contrast to the infrequency of a tender liver and a palpable spleen in arsphenamin jaundice. On the other hand, Ruge<sup>4</sup> does not agree that there are any significant differences in the physical findings of the two conditions.

TABLE III.—FREQUENCY OF IMPORTANT FINDINGS IN CATARRHAL AND ARSPHENAMIN JAUNDICE.

	Catarrhal jaundice,* per cent.	Arsphenamin jaundice. per cent.
Jaundice (clinical) . . . . .	92	100
Bile-stained urine . . . . .	88	87
Nausea . . . . .	88	41
Anorexia . . . . .	82	46
Clay-colored stools . . . . .	80	57
Fever . . . . .	75	36
Vomiting . . . . .	72	49
Headache . . . . .	70	15
Constipation . . . . .	66	18
Abdominal pain . . . . .	60	31
Chills . . . . .	48	12
Pains in extremities . . . . .	34	18
Prostration . . . . .	30	16
Diarrhea . . . . .	15	5

PHYSICAL FINDINGS.

Enlarged liver . . . . .	No comparative	66
Tender liver . . . . .	data	13
Abdominal tenderness . . . . .	"	8
Palpable spleen . . . . .	"	7

\* Recalculated from a table given by Williams (<sup>13</sup>) based on the 700 cases studied by him.

**The Blood.** Some authorities in the past, such as Scott and Pearson,<sup>8</sup> have dismissed the blood picture in arsphenamin jaundice with the mere mention that the white blood-cell count is normal; others, as Lynch and Hoge,<sup>16</sup> Longcope<sup>17</sup> and Silbergleit and Fockler,<sup>18</sup> have cited white blood-cell counts incidentally in isolated case reports. The present study gives more detailed information of the blood in this condition.

Before proceeding, however, to a discussion of the blood picture in arsphenamin jaundice and contrasting it with that of catarrhal jaundice, it is deemed advisable to consider first the normal white blood-cell picture. Miller<sup>19</sup> made an excellent study of the white blood cells of 280 students at Johns Hopkins University; but his results must be partially discarded for the purposes of contrasting with abnormal conditions because of the failure to include a frequency table of the total leukocyte count. Ehrlich's stain was employed to study the blood of some of these students. This must also be reckoned with, because, as he himself showed, the use of this stain tends to lead to a higher count of polymorphonuclears than when one of the modifications of the Romanowsky stain are used,

as was done for the cases of catarrhal and arspenamin jaundice referred to further on. The normal leukocyte counts used in the comparisons given below are based on data for 310 individuals,

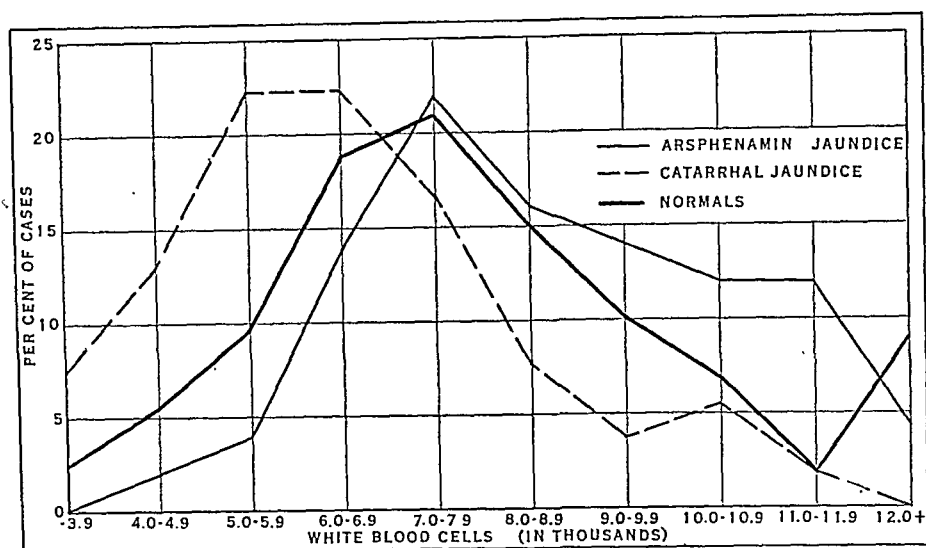


FIG. 1.—Comparison of average leukocyte counts in 50 cases of arspenamin jaundice, 54 cases of catarrhal jaundice and 310 normals.

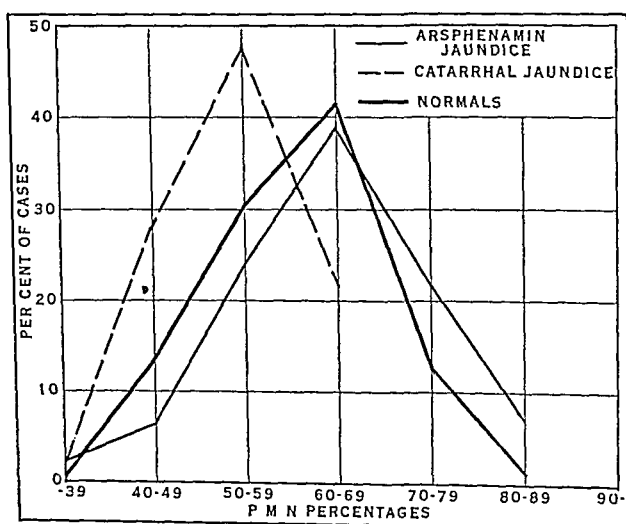


FIG. 2.—Comparison of average polymorphonuclear neutrophil percentages in 46 cases of arspenamin jaundice, 42 cases of catarrhal jaundice and 287 normals.

selected from the studies of Bunting,<sup>20</sup> Galambos,<sup>21</sup> von Torday<sup>22</sup> and Zappa;<sup>23</sup> the polymorphonuclear counts are based on data for 287 individuals, selected from the studies of Bunting,<sup>20</sup> Miller,<sup>19\*</sup> Mehrtens,<sup>24</sup> Emerys-Roberts<sup>25†</sup> and von Torday.<sup>22</sup> All the differ-

\* Data on only 50 students selected, whose bloods were studied by a modification of the Romanowsky stain.

† Data on 50 British students.

ential counts for which data are utilized were made on blood stained by a modification of the Romanovsky method.

The distributions of the average leukocyte counts and polymorphonuclear neutrophil percentages in health and in arsphenamin and in catarrhal jaundice are compared in Figs. 1 and 2. It is obvious from the data recorded in the graphs that the white blood-cell pictures show appreciable differences. Fig. 1 indicates that only 20 per cent of the patients with arsphenamin jaundice have average leukocyte counts below 7000 per c.mm., while 36 per cent of normal persons and 65 per cent of catarrhal jaundice patients have white blood-cell counts below this number. Similarly, Fig. 2 shows that in arsphenamin jaundice 34 per cent of the patients have polymorphonuclear neutrophil percentages below 60, while the corresponding values for normal persons and catarrhal jaundice patients are 45 and 79 per cent respectively.

Furthermore, the data collected for this study are based on a sufficient number of cases to permit of the evaluation of these differences on a statistical basis.

TABLE IV.—COMPARISON OF THE MEAN VALUES OF TOTAL LEUKOCYTES AND POLYMORPHONUCLEAR NEUTROPHIL PERCENTAGES.

	No. of cases.	Mean leukocyte count.	No. of cases.	Mean neutrophil percentage.*
Normal . . . . .	310	7850 $\pm$ 132	287	59.6 $\pm$ 0.55
Arsphenamin jaundice . .	50	8690 $\pm$ 301	46	62.8 $\pm$ 1.70
Catarrhal jaundice† . .	54	6480 $\pm$ 262	42	53.5 $\pm$ 1.29

\* The individual groups of mononuclear cells are not considered here because of the large error that is certain to be present when different individuals classify such cells. Taken as a single group the mononuclear cells in arsphenamin jaundice have a distribution just the reverse of the polymorphonuclear neutrophils, since the polymorphonuclear eosinophils and basophils and other cells form only a very small portion of the total leukocyte count.

†For catarrhal jaundice the data of Jones and Minot<sup>5</sup> and Thewlis and Middleton<sup>6</sup> are combined, excluding the latter's figures for the period before the onset of jaundice.

Table IV shows that the mean leukocyte count in arsphenamin jaundice is 8690 per c.mm. and the standard deviation of this mean, expressed as a plus and minus quantity is 301. The normal mean leukocyte count and its standard deviation is 7850  $\pm$  132 per c.mm. The difference between these two means is 840  $\pm$  329 cells per c.mm., and is 2.6 times its standard deviation. Since any difference in the means of two series is to be considered significant if it is as great or greater than twice its standard deviation, then the above difference certainly has statistical significance. Similarly, the difference between the mean white blood-cell counts in catarrhal jaundice and in normal persons is 1370  $\pm$  293 cells per c.mm. which is 4.7 times its standard deviation. In the case of the two pathologic conditions, this difference is 2210  $\pm$  400 or 5.5 times its standard deviation, and consequently is more significant than the

variation of the mean white blood-cell count of either condition from the normal mean. Similar evaluations of the differences in the mean neutrophil percentages are obtainable from Table IV. They are as significant statistically as those of the corresponding mean leukocyte counts, except that the average neutrophil percentage in arsphenamin jaundice is not sufficiently greater than the normal to be looked upon as definitely abnormal.

An attempt has been made to correlate the level of the leukocyte count with the duration of jaundice. The sparseness of data does not permit of final opinions. The most that can be said is that there is a tendency for higher counts to occur during the first week of arsphenamin jaundice than during the remainder of the course of the diseased state.

The average leukocyte count for the first week is  $11,300 \pm 943$  cells per c.mm., while the average for the remainder of the course is  $9060 \pm 339$ . The difference between these two averages is  $2240 \pm 1002$  cells per c.mm. which also has statistical significance.

From the foregoing discussion, it is evident that in arsphenamin jaundice there is a tendency toward a slight leukocytosis and seldom does there occur a leukopenia with relative lymphocytosis so characteristic of catarrhal jaundice. Only two of the cases of arsphenamin jaundice had both a leukocyte count of less than 7000 per c.mm. with the lymphocytes forming more than 30 per cent of the white blood cells. These observations are supported by the experimental work of Herzog and Roscher,<sup>26</sup> who showed that in chronic arsphenamin poisoning in dogs there is very little alteration in the white blood-cell picture. On the other hand, it is in direct conflict with the statement of Ruge<sup>27</sup> that leukopenia and relative lymphocytosis are found after the first week of arsphenamin jaundice. In spite of his disagreement with the above findings, it is believed that a careful study of the white blood-cell picture will be of distinct value in differentiating between cases of arsphenamin and catarrhal jaundice.

**Conclusions.** 1. The clinical picture of arsphenamin jaundice simulates in many ways that of catarrhal (infectious) jaundice but does differ in some respects. The symptoms in the former are mild and few in number; pyrexia and prostration are rare. Frequently an enlarged and tender liver and less frequently a palpable spleen occur in catarrhal jaundice, while a tender liver and palpable spleen are rare in arsphenamin jaundice.

2. The white blood-cell picture in arsphenamin jaundice is characterized by a slight leukocytosis and a normal differential count, in contradistinction to the characteristic leukopenia with relative lymphocytosis that develops in catarrhal jaundice.

3. The total leukocyte count in arsphenamin jaundice tends to be higher during the first week of jaundice than thereafter.

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## SEROLOGIC STUDIES OF PROTEINURIAS.

## III. THE PRECIPITIN TEST AS AN ADJUNCT IN THE DIAGNOSIS AND PROGNOSIS OF NEPHRITIS.

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FROM preliminary observations of the precipitin reaction, the writer<sup>1</sup> feels that this type of serologic reaction may be of value in the diagnosis of the nephritides. It is interesting to note that nephritis may or may not be associated with definite urinary findings, yet it seems plausible that the urine in a number of cases may present serologic properties that may be impossible to detect by ordinary chemical or microscopic study. Inasmuch as certain extraneous proteins are commonly detected in the urine by the precipitin test, study of urinary proteins by this means seems logical. Uhlenhuth<sup>2</sup> has shown that the precipitin test may be utilized in the identification of different meats. Von Regler,<sup>3</sup> Schmidt,<sup>4</sup> and numerous others have confirmed these results. Gay<sup>5</sup> was able to identify the heart of a deer by this method in a legal case for infringement of its game laws, thereby assisting the State of Massachusetts.

Hektoen and Welker,<sup>6</sup> in their summary, state that euglobulin, pseudoglobulin and albumin of beef, dog, horse and human serums are of one distinct species—specific precipitinogens. They also conclude that precipitin serums produced by injecting serum, blood or albumins may contain specific precipitins for the corresponding serum proteins, and that the antigenic individuality is not the artificial product of the process of separation. Considerable work has been done on the identification of the various proteins in the urine. In scanning the literature, I find that very little work has been done on the identification of nephritic antigens in the urine.

My observations in this series of cases do not agree with the work of Wells.<sup>7</sup> The antigen used, however, was prepared from inflamed human kidney substance. The use of inflamed kidney substance may in some way assist in the formation of antigen that ordinarily would be missing if normal kidney substance had been used. Before preparing the antigen used in this study, the writer prepared one from normal kidney substance and was unable to detect a single positive reaction.

If a patient is suffering with a severe renal damage, the urine usually contains the evidence of this destructive process (for example, renal casts, blood, albumins). Clinical observation has

shown, however, that the amount of this urinary evidence does not run hand in hand with the amount of renal damage. It is well known that large amounts of albumin may be found in the urine where the kidneys are in a relatively normal state. Likewise albumin may be found in the urine in such functional states as alimentary and orthostatic albuminuria. In a given case of nephritis, we may know that the kidneys are undergoing a vast amount of degeneration which is apparently out of proportion to similar damage occurring in other organs. Furthermore, if the kidneys are undergoing destructive change, the by-products are removed mainly by way of the urine. It, therefore, appears reasonable that these broken-down renal proteins may be detected by the precipitin reaction, thereby giving us an index as to the quantitative and qualitative extent of renal destruction. On this working basis, the writer has carried out this test, on the urines of patients that presented a positive albumin test by the acetic acid method. Clinical findings of each patient studied, and allied diagnostic tests were not taken into consideration until the precipitin test was performed. Although the tests performed are few in number, they may give us an insight into the possibilities of the precipitin test as an adjunct in the diagnosis and prognosis of nephritis.

**Preparation of Antinephritic Rabbit Serum Used in the Precipitin Test.** During an autopsy performed by the writer at the Salt Lake County General Hospital, the kidneys were removed from a girl, aged sixteen years, who died of a subacute diffuse nephritis. The autopsy was performed within fifteen minutes after the death of the patient which occurred at 10 P.M., October 24, 1926. The writer treated the patient clinically, and she had all the characteristic symptomatology of the disease. The kidney substance, the weight of which was 385 gm., was immediately iced and ground with 150 gm. of glycerin. Glycerin was used as a preservative, and as a vehicle for emulsification.

To 450 gm. of glycerinated ground kidney substance, 350 cc. of sterile distilled water was added. This mixture was placed in a sterile mortar and ground for a period of thirty-five minutes, then filtered through cotton into a container. After the filtrate had been collected the unfiltered residuum was placed in the sterile mortar and again ground for thirty-five minutes with 100 cc. of 95 per cent grain alcohol. This mixture was again filtered through sterile cotton and the filtrate placed in an evaporating flask. The alcohol was evaporated from the mixture by allowing filtered air to pass into the flask which was kept warm by a water bath. After the alcohol had evaporated, the residuum was added to the aqueous extract and the entire mixture was phenolized to the extent of 0.5 per cent. The filtered emulsion was then ready for administration to the rabbits.

Albino male rabbits were used as recipients for the kidney extract. The extract was inoculated intraperitoneally through the shaved

abdominal wall. When large doses were given, the gravitation method was used. Dosage began with 1 cc. and increased every day or two until the single dosage totaled 25 cc. Three rabbits succumbed during the process of antigen preparation.

The rabbits were bled to death by intracardial puncture. The blood was collected in sterile centrifuge tubes and the serum removed by rapid centrifugation. The clear serum was collected and phenolized to the extent of 0.25 per cent. A titer was not taken during the preparation of the serum because the nephritic extract would not give a clear filtrate. The serum was then sealed in sterile ampules, and was used in the urinary tests.

**Technique of the Precipitin Reactions.** Prior to the precipitin reaction the sensitive rabbit serum was activated by keeping it at body temperature for a half hour. The precipitin reaction was prepared on microscopic slides upon which three paraffin rings were placed. The first paraffin ring contained one drop of filtered urine and one drop of the antigen. Ring No. 2 contained one drop of the antigen as the first control. To the third ring one drop of urine was added as a second control. The mixture and the controls were then studied by means of a low-power microscopic objective. If a reaction were not apparent within twenty minutes after the mixture was made, it was considered negative.

The urinary specimens used in this study, were obtained from hospital cases under aseptic precautions. All presented protein in varying quantities as shown by the acetic acid test. Immediately upon collection each specimen was filtered through sterile cotton and paper and mixed with the antigen. The urine had to be clear in order to make a satisfactory test. For the most part, the urines examined were acid in reaction. From this study, reaction of urine had little or no bearing on the result obtained.

**Observation of Precipitin Reactions in Urines Studied.** Of the 500 cases studied, 143 gave a positive serologic reaction to the nephritic antigen. This is of interest when we note that every specimen examined presented evidence of protein which was detectable by ordinary chemical methods. The main point of interest regarding the positive reactions, however, is that only 152 of the cases presented in this study had clinical or laboratory evidence of nephritis. In the remainder, the presence of urinary protein had no bearing on the diagnosis of the case. Of those presenting evidence of nephritis a positive serologic reaction was present in all but 19. Ten of the 19 negative reactions were present in cases definitely diagnosed as chronic interstitial nephritis. The negative findings in these 10 cases are interesting inasmuch as chronic interstitial nephritis has widely been considered a chronic sclerotic process rather than an inflammatory process. If this consideration be true the nephritic antigen failed in only 9 of the 153 cases that presented evidence of kidney inflammation. Further



SEROLOGIC STUDIES OF PROTEINURIAS: CHART LISTING 500 CASES STUDIED WITH HUMAN NEPHRITIC ANTIGEN.

Diagnosis.	No. cases.	Presenting tube casts.			Presenting evidence of nephritis other than tube casts.	Total clinical nephritis.	Positive precipitin reactions.
		H.	G.	Both.			
Lobar pneumonia . . . . .	9	2	3	0	0	5	4
Postpartum (pregnancy) . . . . .	144	4	3	7	6	20	23
Postoperative . . . . .	119	2	7	10	12	31	38
Paratyphoid . . . . .	1	0	0	0	0	0	0
Pulmonary tuberculosis . . . . .	15	1	0	0	3	4	6
Chronic interstitial nephritis . . . . .	12	3	0	0	9	12	2
Chronic diffuse nephritis . . . . .	11	1	4	3	2	11	10
Eclampsia . . . . .	1	0	0	1	0	1	1
Unknown diagnosis . . . . .	45	1	4	4	0	9	9
Lead poisoning . . . . .	1	0	0	1	0	1	1
Involutonal melancholia . . . . .	1	0	0	0	0	0	0
Cardiac decompensation . . . . .	30	4	2	6	7	19	21
Secondary anemia . . . . .	2	0	0	0	1	1	1
Infant feeding . . . . .	4	0	0	1	0	1	1
Acute bronchitis . . . . .	1	0	0	0	0	0	0
Vincent's angina . . . . .	1	0	0	0	0	0	0
G. C. salpingitis . . . . .	1	0	0	0	0	0	0
Bronchopneumonia . . . . .	1	0	0	0	0	0	0
Erysipelas . . . . .	1	0	0	0	0	0	0
Bronchial asthma . . . . .	1	0	0	0	0	0	0
Senile gangrene . . . . .	1	0	0	0	0	0	0
Bichlorid of mercury poisoning . . . . .	1	0	0	1	0	1	1
Lung abscess . . . . .	1	0	0	0	0	0	0
Bacteriemia . . . . .	3	0	0	2	0	2	2
Scarlet fever . . . . .	5	0	1	0	0	1	1
Chronic infectious arthritis . . . . .	4	0	0	1	1	2	2
Rheumatic fever . . . . .	4	0	0	0	1	1	1
Subacute nephritis . . . . .	6	1	1	2	2	6	4
Inevitable abortion . . . . .	1	0	0	0	1	1	1
Chronic mastitis . . . . .	1	0	0	0	0	0	0
Delirium tremens . . . . .	1	0	0	0	0	0	0
Cervical hemorrhage . . . . .	1	0	0	0	0	0	0
Pyelitis . . . . .	1	1	0	0	0	1	1
Acute epididymitis . . . . .	2	1	0	0	0	1	1
Diphtheria . . . . .	1	0	0	0	0	0	1
Orchitis . . . . .	1	0	0	0	0	0	0
Cystitis . . . . .	5	1	0	0	0	1	1
Renal calculi . . . . .	2	0	0	0	0	0	1
Prostatitis . . . . .	3	0	0	0	0	0	1
Gastric ulcer . . . . .	8	0	0	0	1	1	1
Otitis media . . . . .	2	1	0	0	1	2	1
Chronic hypertension . . . . .	4	0	0	2	2	4	2
Acute nephritis . . . . .	4	0	0	4	(4)	4	4
Carcinoma . . . . .	5	0	0	0	1	1	1
Sarcoma . . . . .	2	0	0	0	0	0	0
Tuberculosis of hip . . . . .	1	0	0	0	0	0	0
Puerperal sepsis . . . . .	1	0	0	0	0	0	0
Tonsillitis . . . . .	12	0	1	2	1	4	5
Diabetes mellitus . . . . .	6	0	1	0	1	2	1
Rheumatic fever . . . . .	2	0	0	1	0	1	1
Maxillary sinusitis . . . . .	2	1	0	0	0	1	1
Typhoid fever . . . . .	4	0	0	0	0	0	0
Total . . . . .	500	24	27	48	52	152	143

study will possibly lower this percentage of error. All the 4 cases of acute nephritis in this series gave strongly positive reactions, while 4 of the 6 cases of subacute nephritis gave positive reactions. In both the acute and subacute nephritis however, when the tube casts were detectable, in the specimen examined a precipitin reaction was noted. Ten of the 11 cases of chronic diffuse nephritis gave a positive serologic reaction. Positive serologic reactions were present in 19 cases of this series which failed to present clinical or laboratory evidence of nephritis.

**Summary.** 1. It appears from this preliminary study of urines which present protein chemically, that the precipitin test offers a possible adjunct as a diagnostic and prognostic agent in the nephritides.

2. This study tends to support the view that relegates the chronic interstitial type of nephritis to a noninflammatory classification.

3. This serologic study tends to support the idea that in certain cases of nephritis a protein of nephritic origin is present in the urine.

4. The antigen prepared from inflammatory kidney substance seems to contain sensitive bodies that are apparently lacking in an antigen prepared from nonpathologic kidney substance.

5. The urines giving negative precipitin reactions were apparently free from nephritic protein. The protein which they contain had evidently taken origin from sources other than the kidney.

6. It appears from this study that the presence of protein in the urine in the vast majority of cases takes origin from tissue sources other than the kidney.

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### THE BLOOD SEDIMENTATION TEST IN EXPERIMENTAL POLIOMYELITIS.

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IN 1918, Fahraeus published his observation that the red blood corpuscles in citrated blood have a different gravitation rate. An acceleration of this sedimentation rate was especially noted in the blood of gravid women. The German gynecologist, Linzenmeier,

during his investigations in his clinic, found that the sedimentation test may be of great value in the differential diagnosis between inflammatory infections of the adnexa and other noninflammatory affections of the tubes, such as benign tumors, myomas, dermoids, cysts, and so forth. The conclusions of Linzenmeier were that in every inflammatory condition of the tubes there is a marked acceleration of the sedimentation time.

The work of Linzenmeier was followed by a great number of papers on this problem, and in the "*Ergebnisse der Inneren Medizin und Kinderheilkunde*," for 1924 there was published a general review of this question which occupies 155 pages.<sup>1</sup> The appendix occupies 10 pages with references to 324 different papers written on the same subject. This reference list, however, is incomplete as it does not quote the many French and American works.

The sedimentation test has been tried in practically all pathologic conditions including even nervous and mental diseases like melancholia, dementia precox, and so forth.

The general conclusion of these papers is that there exists a marked acceleration in the sedimentation time in all febrile conditions, whether acute or chronic, especially in surgical cases and cases of malignant tumors. From the personal observations of the writer, it is evident that even in small tumors like epithelioma of the lips and tongue, the sedimentation of the red blood corpuscles is very rapid. In all cases of syphilis of the nervous system—*tabes*, general paralysis, arteriosclerotic cerebral processes—the sedimentation rate is accelerated. However, in the nonsyphilitic affections of the nervous system such is not the case. In 18 patients having encephalitis, Lorenz and Berger determined the sedimentation speed of erythrocytes: in some of them the speed was accelerated; in others retarded. They concluded, therefore, that the test was of no diagnostic value in encephalitis.

Important and interesting results have been obtained in tuberculous affections, and, according to many authors the test may give valuable data in the diagnosis and prognosis of this disease. The changes in the sedimentation time may furnish indications of the influence of the different therapeutic measures like pneumothrax and others.

It is not the purpose of this paper to discuss in detail the different theories relating to the etiology of this phenomenon. We shall only briefly enumerate the more important of these theories.

The sedimentation of the red blood corpuscles closely depends on the colloido-chemical and electrical process which ordinarily determines the stability of the suspensions. According to this theory, the stability of any cellular suspension depends on the electrical charge of the particles with equal potentiality. Since they have the same polarity, they repel each other and remain in suspension. Erythrocytes with a rapid sedimentation time are supposed to have a re-

duced charge, while the reverse is true of erythrocytes with a slow sedimentation rate. In fact, the former condition is found to exist in blood of gravid women. The reason for this is found in the plasma which has the property to reduce the charge.

Hoeber has also demonstrated that usually erythrocytes have a negative polarity, that is, they are attracted to the anode (+). If the erythrocytes settle more rapidly, it is because of a reduction in their potentiality.

In summary, according to this theory, the sedimentation is conditioned by the electrical discharge of the erythrocytes. This discharge is made by the appearance in the plasma of a positive charged body. This body may be removed by different absorbent solutions.

Starlinger sees a close connection between the agglutination capacity and the sedimentation rate. He also observes that there is an increase of fibrinogen in the suspension with a high sedimentation speed and a decrease in those cases with a low sedimentation speed.

Löhr admits that the sedimentation time is proportional to the intensity of the cellular destruction and absorption of the metabolic products (cancer).

Von Oettingen<sup>2</sup> brings out that the sedimentation time is a function of the physical structure of the colloids of the plasma, particularly of the proteins.

In their recent researches, Hoeber and Mond<sup>3</sup> sustain the capillaro-electrical theory of Fahraeus. They admit that in all cases where there is an increase in the sedimentation time, the increase comes about because the globulins take more or less the place of the albumins in the absorbent membrane of the erythrocytes. The isoelectric point of the globulins, that is, the point at which the tendency for flocculation is highest, is nearer to the neutral reactions of the blood than the isoelectric point of the albumins. It becomes clear why in erythrocytes rich with globulins there is a marked tendency for flocculation and agglutination.

The solubility of the protein bodies, and especially the surface tension of the red corpuscles, have to be taken into consideration.

The methods used by different authors for the determination of the sedimentation rate are not similar and therefore it is quite often impossible to compare their findings. Many modifications have been made by German and French experimenters in the test procedures. In this country, a simple method was devised by Zeckwer and Goodell,<sup>4</sup> but this process requires 8 cc. of blood taken from a vein. Obviously, in a test which has only a secondary clinical diagnostic value, it is very desirable to avoid drawing so much blood, especially as patients often object to giving their blood.

These modifications relate to the concentration of sodium citrate, to the amount of blood, diameter and height of the test tube. Obviously, the less blood, the more practical is the test. This is

the reason why there have been offered micromethods requiring only one or several drops of blood.

Yet the most practical procedure seems to be that of Linzenmeier, whose technique we have used.

**The Linzenmeier Technique.** The necessary outfit: (a) One cubic centimeter hypodermic syringe, marked with 0.1 cc. divisions. (b) Sedimentation tubes of 6.5 cm. length and 5 mm. diameter, with a capacity slightly over 1 cc. The space between the 1-cc. mark and the 18-mm. mark bears two other divisions—6-mm. and 12 mm. We designate the 6-mm., 12-mm. and 18-mm. points as I, II, III, respectively.

Instruction for the Linzenmeier technique is as follows:

1. Draw into the syringe 0.2 cc. of the 5 per cent solution of sodium citrate.

2. To make the total contents of the syringe 1 cc., draw into it 0.8 cc. of blood.

3. The tube in which the sedimentation test is to be carried out must be kept perfectly dry.

4. Slowly mix in the tube the blood and sodium citrate solution. The marginal level in the tube must be exactly at the 1-cc. mark.

5. Note the length of time taken for the red blood cells to settle to point III (18 mm.) on the tube.

During the course of our work on experimental poliomyelitis (vaccination and neutralization tests), we had a certain number of monkeys which came down with this experimental disease. In some of them, in line with the routine blood examinations, we performed the sedimentation test. The blood was taken the first or second day of the disease, when the animals showed definite symptoms of paralysis. Previously we determined the sedimentation time of blood taken from normal monkeys. As seen from Table I the average sedimentation time was nineteen hours and thirty-two minutes.

TABLE I.—READINGS IN A GROUP ON NORMAL MONKEYS.

Number of monkey.	Sedimentation time in minutes to 18-mm. mark.	Number of monkey.	Sedimentation time in minutes to 18-mm. mark.
77	1330	101*	855
78	960	105	1140
79	980	109	1340
79	900	109	1260
85	1380	109	1410
85	1320	117*	1130
85	1070	119*	1180
87	1200	133	1240
93	1405	115	920
93	1265		
94*	1150		
94	900		

14 monkeys

21 sedimentation tests

Average sedimentation time: 19 hours and 32 minutes.

The repeated tests of the same monkey were made on different days.

\* See sedimentation time of the same monkey in Table III.

These figures show that the sedimentation time in normal monkeys closely approaches the time necessary for sedimentation of normal human blood. In fact, Löhr,<sup>5</sup> in his examinations of human blood, found that the sedimentation time for normal men (time required to reach the 18-mm. mark) is from 1200 to 1400 minutes, and for nonmenstruating women from 850 to 1000 minutes. Friedländer<sup>6</sup> obtained similar results, that is, 1000 to 1200 minutes for healthy men; 600 to 1000 minutes for healthy women.

There were in the animal room at different periods a certain number of monkeys with spontaneous tuberculosis. We had occasion to perform the sedimentation test on them and the results strikingly confirmed the findings in human bacillary infections. The diagnosis of tuberculosis was in each case confirmed by a postmortem examination. All cases showed extended tuberculous lesions in one or both lungs. In addition to the lung pathology, there were in almost all cases other localizations. The most frequent were tuberculosis of the spleen, liver, mesenteric glands and intestines. In one animal we found only disseminated nodules, but in a great majority of them death was due to extended lung invasions. Table II will show the findings in this group of monkeys.

TABLE II.—SEDIMENTATION REACTIONS IN A GROUP OF MONKEYS HAVING TUBERCULOSIS.

Number of monkey.	Sedimentation time in minutes.
52	120
52	110
52	180
65	105
60	80
60	80
60	85
60	75
80	70
84	65
84	45
84	20
84	30
84	65

5 monkeys

14 sedimentation tests

Average sedimentation 1 hour and 20 minutes.

The repeated tests of the same monkey were made at different days.

Experimental poliomyelitis being practically a fatal disease for monkeys, a great number of them die in the first four or five days after the onset of the disease. Yet, from time to time, due to the use of a virus of lower virulence or artificially modified, the disease follows a milder course and the animal recovers with residual paralysis and atrophy. It is interesting to note that in three of these animals the sedimentation tests made several months after the disappearance of the acute symptoms, showed a normal sedimentation time. Table III shows the findings for the poliomyelitis monkeys.

TABLE III.—SEDIMENTATION TIME IN CASES OF EXPERIMENTAL POLIOMYELITIS.

Number of monkey.	Sedimentation time in minutes.	Number of monkey.	Sedimentation time in minutes.
89	45	125	100
94*	250	127 <sup>1</sup>	405
101*	210	127	140
101*	140	128	130
101*	180	146	105
104	55	146	255
104	45	200	190
108	190	224	125
110	135	231	200
111	90	254	70
111	70	254	120
111	390	278	135
117*	120	278	
118	205		
118	235		
119*	95		
120	195		

\* See sedimentation time of the same monkey in Table I.

20 monkeys; 29 sedimentation tests; average sedimentation time two hours and thirty-nine minutes. The repeated tests of the same monkey were made at different dates of the acute disease.

We have also performed the sedimentation test on three monkeys which after a long number of months in captivity developed a general debility (loss of appetite, weakness, slowness in motion, pallor, conjunctival and facial edemas). In all of the three monkeys the sedimentation time was extremely rapid. We had also a few instances of monkeys with an infected skin which resulted in large superficial ulcerations of the skin, on the spine, and on the abdomen. These cases also showed a very rapid sedimentation time.

TABLE IV.—READINGS IN MISCELLANEOUS CASES.

Number of monkey.	Diagnosis.	Sedimentation time in minutes.
264	General debility	40
264	General debility	35
276	General debility	40
276	General debility	25
270	General debility	10
270	General debility	30
		20
		35
190	Infected skin	60
161	Infected skin	80
161	Infected skin	10
161	Infected skin	90

**Summary.** The sedimentation time for normal healthy monkeys was determined and found to be nineteen hours and thirty-two minutes.

The sedimentation time of monkeys sick with poliomyelitis is considerably shorter, giving an average of two hours and thirty-nine

minutes, and showing a marked difference from the sedimentation time of normal monkeys.

The sedimentation time for monkeys sick with tuberculosis, general debility of undetermined nature and superficial infection is still shorter, namely, one hour and twenty minutes.

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### TEMPORARY EDEMA OF THE FACE FOLLOWING TREATMENT FOR EXOPHTHALMIC GOITER.\*

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THERE is often a remarkable change in the face of a patient with exophthalmic goiter within a few weeks after a subtotal thyroidectomy. It appears to have gained more in proportion than any other part of the body, and, in striking contrast to its preoperative angular contour, has rapidly become round and puffy.

Some of the first patients that we noticed had a low basal metabolic rate, and complained of some or all of the following symptoms: Weakness, lassitude, ease of fatigue, chilliness, dryness of the skin and falling out of hair. This, together with the edematous appearance of the face, led us to believe that they had mild myxedema, later, concluding that it was only temporary, because either with or without a brief course of thyroid medication, these signs and symptoms disappeared within a few weeks or months and did not recur.<sup>4</sup>

\* This study was aided in part by a grant from the Proctor Fund of the Harvard Medical School, for the Study of Chronic Diseases.



However, as time elapsed and more data were collected on these and other cases, we began to question the diagnosis of myxedema. It was found that, during the period of puffiness of the face, the patients could be grouped as follows:

1. Those with additional signs and symptoms suggesting myxedema and a low basal metabolic rate. In this group, there were two types of low metabolism: (a) Permanent. The basal metabolism remained at a low level without medication on the disappearance of the syndrome suggesting myxedema. Case 1 (see Fig.

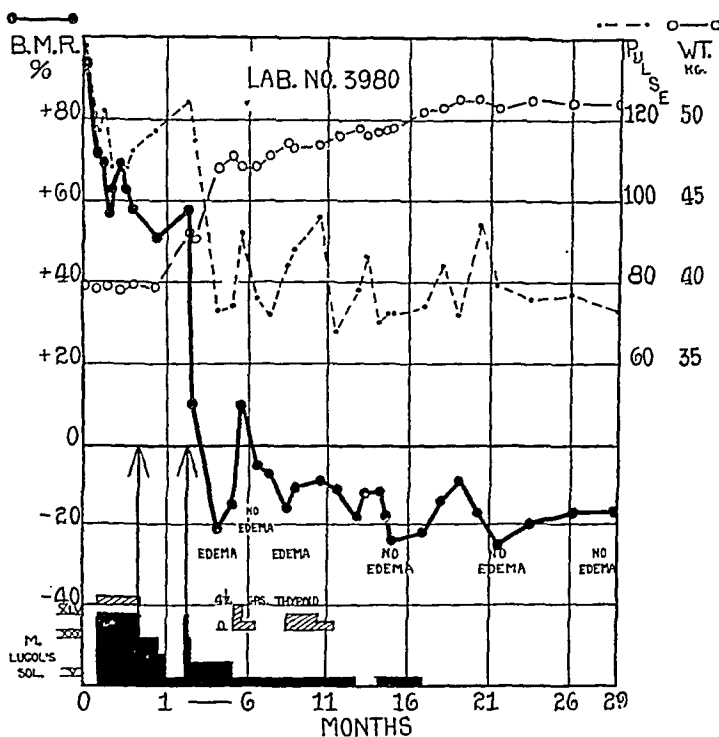


FIG. 1.—Case I. Mrs. D. C. Aged thirty-two years. Puffiness of the face, weakness, fatigue, dopiness, chilliness and backache, in association with a low basal metabolic rate, occurring two months after the second of two hemithyroidectomies (arrows) for exophthalmic goiter. These signs and symptoms disappeared twice on thyroid therapy, but did not recur following the second omission of thyroid, in spite of the fact that the metabolism remained low.

1) and Case 2 (see table): (b) Temporary. The basal metabolism rose to a standard normal level with the disappearance of the syndrome suggesting myxedema. Case 3 (see Fig. 2) and Cases 4 and 6 (see table).

2. Those with additional signs and symptoms suggesting myxedema and a standard normal basal metabolic rate. Case 5 (see Fig. 3), and Case 7 (see table).

3. Those in which the puffy face was almost the only suggestion of myxedema, with a standard normal basal metabolic rate. Case 8 (see Fig. 4) and Case 9 (see table).

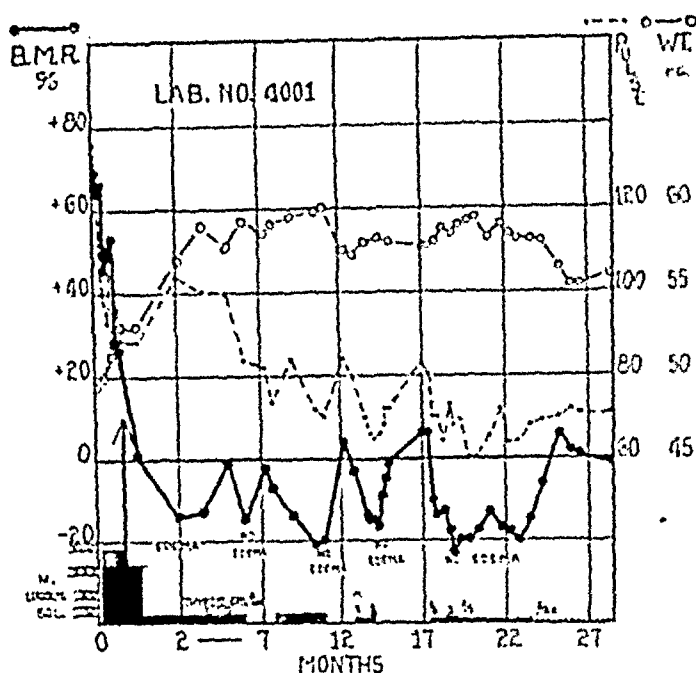


FIG. 2.—Case 3. Mrs. V. P. Aged thirty years. Repeated production of temporary low basal metabolism by administration and omission of iodine, following subtotal thyroidectomy (arrow) for exophthalmic goiter. At the time of the first low metabolism the patient had puffiness of the face and legs, falling hair, dry skin and was weak, chilly and dozey. At the time of her subsequent low metabolisms (one of which lasted six months), she had none of these signs or symptoms and was less nervous than when her metabolic rate was standard normal.

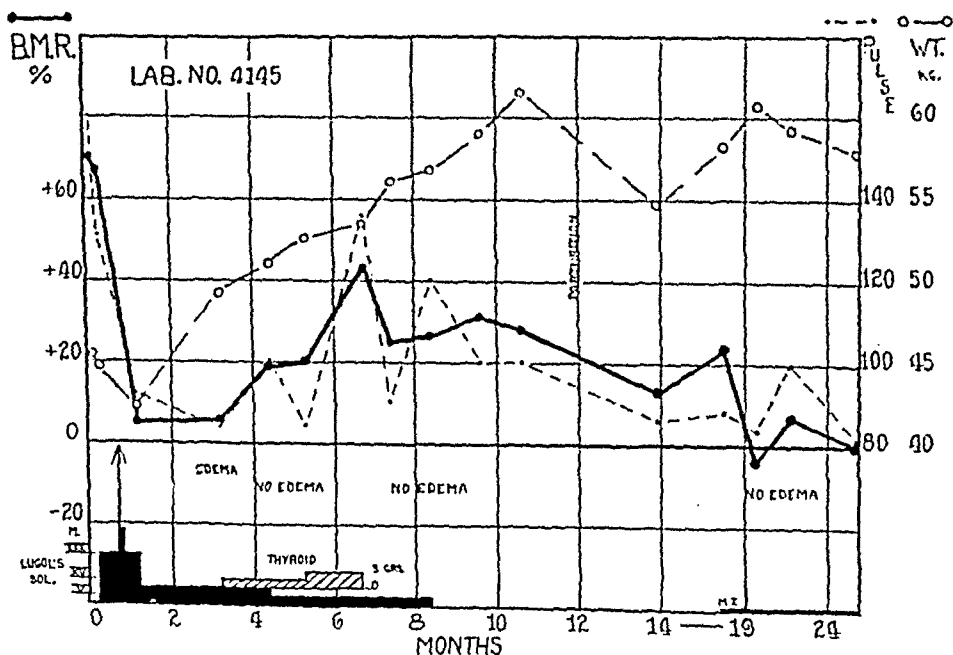


FIG. 3.—Case 5. Mrs. M. K. Aged thirty-nine years. Puffiness of the face, falling hair, weakness, dopiness and marked sensitivity to cold, in association with a standard normal basal metabolism, occurring two months after a subtotal thyroidectomy (arrow) for exophthalmic goiter. These signs and symptoms cleared up on thyroid therapy and did not recur when it was omitted.

CASES\* SHOWING TEMPORARY EDEMA OF THE FACE FOLLOWING TREATMENT FOR EXOPHTHALMIC GOITER.

Case No.	Description.	Date.	B. M. R. per cent.	Pulse.	Wt. Kg.	Treatment.	Clinical notes.
1	Mrs. D. C. (See Fig. 1)						
2	Mrs. A. G., age 24 years. Lab. No. 3768	1/21/26 1/23/26 1/25/26 1/29/26 1/30/26 2/ 2/26 2/11/26 2/14/26 3/ 4/26 4/ 1/26 4/ 6/26	+49 ... +41 ... +16 +8 ... -13 ... -11	114 ... 107 ... 78 74 ... 68 ... 62	51.3 ... 51.5 ... 51.6 51.4 54.9 ... 59.9	Lugol's solution, m X t. i. d. Lugol's m V t. i. d. <i>Subtotal thyroidectomy</i> Lugol's m X t. i. d. Lugol's m X daily Lugol's m V daily Lugol's omitted Lugol's m X t. i. d.  Lugol's m V b. i. d. Armour's thyroid, grs. Iss b. i. d.  Thyroid omitted  Thyroid, grs. Iss b. i. d.  Lugol's m V daily Lugol's m V daily Thyroid omitted  Lugol's omitted	Exophthalmic goiter.       No thyrotoxicosis.  Face puffy. Numbness and tingling of extremities. Weak, dopey, ambitionless. Felt bloated.  Puffiness gone. Definite improvement in other symptoms. Hair falling out. No puffiness of face. Practically symptom free.  Face puffy. Skin slightly dry. Chilly. Weak spells. Puffiness gone. No other signs or symptoms present. Well. Same.
		4/13/26 4/29/26  5/13/26 6/ 3/26 6/16/26 6/25/26 7/16/26 7/31/26 8/15/26 9/ 8/26 10/27/26 12/16/26 1/13/27 2/10/27 3/10/27	-16 + 1  +9 -4 -21 -18 -4 +5 ... -4 +5 -19 -23 -19 -14	72 70  72 58 56 63 72 68 ... 57 76 62 55 56 72	60.9 59.2  58.1 60.5 61.3 60.9 59.3 58.3 ... 58.9 59.9 62.1 62.1 62.7 61.3		

		4/28/27 6/9/27 7/9/27 8/13/27 11/3/27 1/19/28 3/8/28 5/24/28 7/27/28	-14 -18 -18 -14 -10 -13 -17 -14 -12	60 66 63 68 62 64 62 59	61.4 61.8 61.6 60.9 61.3 60.3 61.5 63.3 61.3	Lugol's m V daily Lugol's omitted  Lugol's m I daily  Lugol's omitted	No puffiness of the face. Skin soft and warm. Lots of energy. Did not mind cold.  Well. No puffiness of face or other signs or symptoms suggesting myxedema.
3	Mrs. V. P. (See Fig. 2)						Exophthalmic goiter.
4	Mrs. S. L. Age 22 years. Lab. No. 4450	1/13/27 1/14/27 1/17/27 1/21/27 1/25/27 1/27/27 1/31/27 2/2/27 3/9/27  3/30/27 4/9/27 4/30/27 5/21/27  6/21/27 10/22/27 12/10/27 1/9/28 1/23/28 2/20/28 4/30/28  10/13/28	+31 +12 +7    -11 -25  -11 -17  -9 -23  -13 -3 -15 -13 -23	111 104 76   70 72  72 64  72 72  70 68 68  82	54.2 53.9 54.3   55.5 60.9  61.7 61.5  60.9 63.0  67.5 68.6 67.4 67.2 71.1  74.7	Lugol's solution, m X t. i. d.  <i>Subtotal thyroidectomy</i> Lugol's m XV t. i. d. Lugol's m X t. i. d. Lugol's m V b. i. d. Lugol's omitted  Lugol's m V daily  Lugol's omitted  Lugol's m V daily Lugol's omitted Lugol's m I daily Lugol's omitted  	

Case No.	Description.	Date.	B. M. R. per cent.	Pulse.	Wt. Kg.	Treatment.	Clinical notes.
6	Mrs. J. LaF. Age 29 years. Lab. No. 485	1/14/20	+55	90	52.5	.....	Exophthalmic goiter.
		1/16/20				<i>First Roentgen ray treatment</i>	
		2/7/20	+18	64	49.5	<i>Second Roentgen ray treatment</i>	
		2/9/20	+16	56	49.5	<i>Third Roentgen ray treatment</i>	
		3/1/20				<i>Fourth Roentgen ray treatment</i>	
		3/22/20				Thyroid, grs. Iss daily	Marked clinical improvement. Face and hands puffy. Felt bloated, dull and dopey.
		4/29/20	-11	52	63.0		Improved. Symptoms suggesting myxedema developed again.
		5/14/20	+1	48	63.5	Thyroid, omitted	
		5/20/20	-11	48	63.8	Thyroid, grs. Iss every other day	Face not puffy. No symptoms suggesting myxedema.
		6/19/20	+3	52	64.5	Thyroid omitted	Well.
		7/28/20	+10	52	63.5		
		9/28/20	+13	52	62.0		
		11/29/20	+11	54	62.0	.....	
		5/5/21	+21	60	62.5		
		12/8/21	+11	56	60.5	.....	Four months pregnant. Well. No puffiness of face or other signs or symptoms suggesting myxedema.
		3/21/25	+12	60	71.0		
7	Mrs. H. M. Age 28 years. Lab. No. 4137	8/2/26	+40	104	58.3	.....	Exophthalmic goiter.
		8/4/26	+49	120	58.1		
		9/8/26	+55	112	57.9	Lugol's solution, m XLV daily	
		9/10/26	...	100	56.6	<i>Subtotal thyroidectomy</i>	
		9/16/26	+24			Lugol's omitted	
		9/21/26	-5	80	57.3	Lugol's m V daily	Much improved. Face puffy. Slight pitting edema of ankles. Felt bloated. Sensitive to cold. Somewhat weak and dopey.
		9/29/26	-2	80	65.6		Puffiness definitely decreased. Stronger.
		10/27/26	...			Lugol's omitted	Same.
		12/21/26	+4	72	66.9	Lugol's m V daily	Stronger and brighter. Felt less bloated.
		12/27/26	-12	70	66.3	Thyroid, grs. III daily	Puffiness gone.
		3/4/27	-5	76	65.1	Lugol's omitted	
		4/12/27	+14	84	60.8	Thyroid omitted	
		5/3/27	-8	80	59.5		

S	Miss A. P. Y. (See Fig. 4)	5/24/27 6/14/27 7/14/27 11/10/27 11/22/27 3/19/28 7/24/28	-5 +8 +4 -3 +5 +1	78 88 84 93 88 88	60.0 61.3 64.7 65.1 65.9 71.9	Lugol's, m V daily Lugol's omitted Lugol's m V twice weekly Lugol's m V daily Lugol's omitted .....	No evidence suggesting myxedema.  Perfectly well.  Well. No puffiness of face or other signs or symptoms suggesting myxedema. Pregnant.
9	Miss E. A. C. Age 19 years. Lab. No. 4199					.....	Exophthalmic goiter.
		9/20/26	+68	124	43.7	Lugol's solution, m XV daily	Much improved. Face puffy. No other signs or symptoms suggesting myxedema. Puffiness of face decreased. Tired a little easily; Flesh "softer."  No symptoms suggesting myxedema. Puffiness gone. Question of residual thyrotoxicosis. Puffiness completely gone from face.  Unusually well. Well. No puffiness of face or other evidence suggesting myxedema.
		9/25/26	+91	135	43.7		
		9/27/26	+74	110	42.3	Lugol's m XXX daily	
		9/28/26	+76	106	42.0		
		10/ 2/26	+39	80	43.1	<i>Subtotal thyroidectomy</i>	
		10/ 7/26				Lugol's m XV daily	
		10/13/26					
		10/14/26	+7	76	41.5	Lugol's m V daily	
		10/22/26	+18	90	52.6	.....	
		10/26/26					
		11/24/26	+10	72	52.9	Thyroid, grs. III daily	
		12/31/26	+28	66	50.6	Thyroid, omitted. Lugol's m II daily	
		1/25/27	+6	76	50.7	Lugol's omitted	
		3/15/27	+6	60	49.0	Lugol's m V daily	
		5/19/27	+6	68	47.3	Lugol's omitted	
		7/ 5/27	+21	88	46.6		
		11/ 1/27	+11	84	46.1	Lugol's m I daily	
		11/22/27	+10	76	46.3		
		1/26/28	+5	77	44.5	.....	
		4/13/28	+8	86	42.6	Lugol's omitted	
		7/23/28	+12	80	45.1		
		10/18/28					

\* Some of these cases have been reported before as follows:

- Case 1 is Case 15 in (2).  
 Case 2 is Case 14 (Fig. 5) in (2).  
 Case 3 is Case 27 (Fig. 4) in (1) and also Fig. 5 in (7).  
 Case 6 is Case 6 in (4); Case 1 in (5); and Lab. No. 485 in (6).  
 Case 9 is Fig. 36 in (8).

Thus, a low metabolism was not an essential part of the picture. Moreover, a further study of the cases in Group I indicated that in many instances the low metabolism was a normal one for the particular patient. In Group Ia, as shown in Fig. 1, after the disappearance of the puffiness of the face and other signs and symptoms, the patients, without medication, were apparently normal, although the basal metabolism remained low. The latter was evidently their normal metabolic level, just as a low metabolism appears to be normal for some healthy persons who have never had thyrotoxicosis. (This and related cases are discussed in detail in a previous paper<sup>2</sup>.) In Group Ib, as shown in Fig. 2, subsequent temporary low metab-

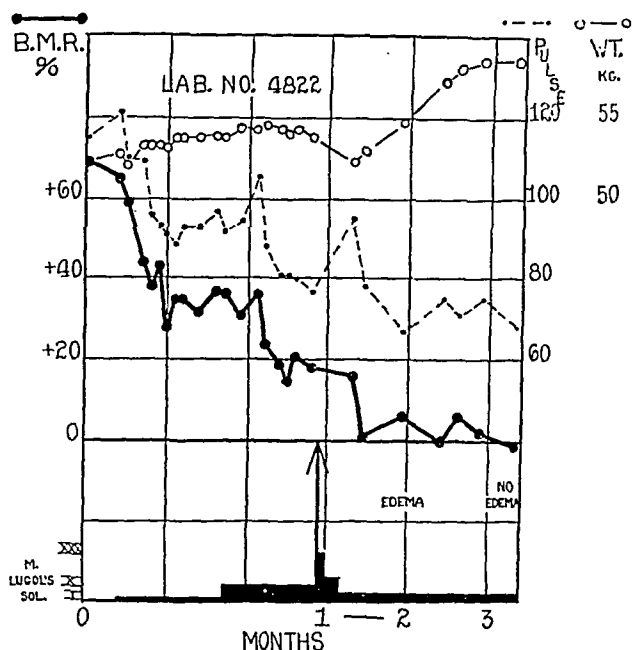


FIG. 4.—Case 8. Miss A. P. Y. Aged twenty-one years. Marked puffiness of the face with a standard normal basal metabolism, occurring one month after subtotal thyroidectomy (arrow) for exophthalmic goiter. There were no other signs or symptoms suggesting myxedema, except falling out of hair. Within one month the puffiness disappeared without medication.

olism in some instances could be produced repeatedly, and for long periods of time, by the administration and omission of iodine, yet there was no return of the puffiness of the face or any other signs or symptoms suggesting myxedema. The patients felt at their best when the metabolism was low. Consideration of the effect of iodine on basal metabolism and clinical symptoms, as discussed in detail in another article,<sup>1</sup> led to the conclusion that at least in cases of this type,<sup>5</sup> the low metabolism is the normal metabolic level, and the standard normal metabolism a level indicating a mild thyrotoxicosis. Thus, if this interpretation of these low metabolic rates be correct, nearly all the cases in our series had a metabolism (either standard or low) which was normal for them during the period when

they clinically suggested mild myxedema. Even if a normal metabolism and temporary underfunction of the thyroid could be associated under certain circumstances, one would expect such a combination to be the exception rather than the rule.

In some instances, the appearance of the face was so distinctly edematous that there seemed to be little doubt that the puffiness was due to edema and not to fat. This conclusion was further upheld by the fact that in some cases the body weight increased while the puffiness was disappearing from the face. It is highly improbable that newly acquired fat would be redistributed in such a manner.

The edema has the appearance of being predominantly facial. Although the body weight may not have reached its pretoxic level, the patient frequently states "I was never so fat in the face in my life." Unfortunately, it is sometimes very difficult to detect a generalized nonpitting edema. There are observations which suggest that it may be present. In a few instances, one got the impression that the tissues felt firmly distended and that this condition subsequently yielded to the more elastic, pliable, normal consistency. One patient had nonpitting edema of the hands as well as of the face. She and four others complained of feeling bloated. Two cases had some swelling of the legs. The question of whether the edema be generalized or limited to the face is a very important one. If it could be proved that it was general, much of the uncertainty about making a diagnosis of myxedema would be eliminated. The thyroid is a very important gland with reference to water balance. It would be only reasonable to attribute a temporary general edema, unaccompanied by evidence of cardio-renal damage, occurring following the removal of a large portion of the thyroid, to a temporary lack of thyroid secretion during the period of adjustment of the gland remnant. Dr. E. P. Richardson<sup>11</sup> suggests that the edema may be entirely facial and due to a temporary blockage of the lymphatics of the neck by scar tissue forming at the site of operation, or due to temporary destruction of these lymphatics by Roentgen ray therapy. These conditions in themselves may be sufficient to produce edema of the face, or they may be contributing factors, acting in combination with a general tendency toward edema.

With regard to the the signs and symptoms which often accompany the facial edema, there is the possibility that the weakness and lassitude constitute a syndrome liable to follow any major operation. Falling out of hair often occurs for a time after thyroidectomy without any other evidence of myxedema. Taken singly, most of these symptoms could be interpreted as due to some other cause than myxedema; but in combination, as was the case in most of our series, they favor this diagnosis.

Additional evidence in favor of the diagnosis of myxedema was the reaction to thyroid therapy in Cases 1 (Fig. 1), 2, and 6. This



resembled the reaction to thyroid in typical myxedema, that is, the edema disappeared; usually the patient lost some weight; the accompanying signs and symptoms cleared up; and the basal metabolism rose to standard normal. On the first omission of thyroid, the syndrome suggesting myxedema recurred. Incidentally, whether the diagnosis be myxedema or not, the bearing on thyroid therapy is the same. Although the syndrome eventually clears up spontaneously, thyroid is indicated as an aid to this end. However, it should be omitted in a few months' time, in order to ascertain if it be still necessary for the patient's welfare.

Thus, against the diagnosis of myxedema are the following:

1. Nearly half of the cases had standard normal basal metabolic rates; moreover, in several of the cases with a low metabolism, this could be interpreted as the patient's normal metabolic level.

2. The edema of the face may be just as pronounced without any other evidence of underfunction of the thyroid, as with the typical clinical picture of myxedema.

3. The edema may be entirely facial: at least it cannot be proved definitely that it is generalized.

4. Accompanying signs and symptoms, such as weakness and fatigue, may be sequelæ of any operation and not peculiar to thyroidectomy.

In favor of the diagnosis of myxedema, are the following:

1. The edema of the face is in several cases accompanied by a low basal metabolic rate and a clinical picture which so strongly suggests mild myxedema that such a diagnosis seems fully justified in these instances, particularly as the circumstances are so propitious for its occurrence.

Cases showing the same clinical picture, but with a standard normal basal metabolic rate, and cases showing facial edema as practically the only abnormality, may be variations of mild myxedema.

2. In some cases there are suggestions that the edema may be generalized and not limited to the face.

3. The effect of thyroid therapy is usually similar to that in definite myxedema.

In view of the above considerations, until further light is thrown upon the subject, we prefer to call the syndrome a temporary edema rather than a temporary myxedema.

The only estimate of the incidence of this temporary edema which can be ventured is that, during the year 1926, it was present in at least 16 per cent of the cases of exophthalmic goiter followed after treatment by surgery or by Roentgen ray in this hospital.<sup>6</sup> As discussed elsewhere<sup>3</sup>, the uncertainty of diagnosis makes it impossible to give any estimate of the incidence of true temporary myxedema following treatment for thyrotoxicosis. If the cases in this series be temporary myxedema, then the latter is a fairly common occurrence;

if they be a temporary edema of some other nature, then temporary myxedema is a very rare sequel to treatment for toxic goiter.

**Summary.** Nine cases are presented showing temporary edema of the face following treatment for exophthalmic goiter. The nature of this edema is discussed.

**NOTES.**—Some of these cases have been reported by us as temporary myxedema,<sup>1,2</sup> but this diagnosis was later modified.<sup>3</sup> A similar case (Case 6 in this study), in which the diagnosis of temporary myxedema seemed justified, was previously reported from this clinic by Means,<sup>4</sup> Seymour<sup>5</sup> and Means and Holmes.<sup>6</sup>

There is another type of case in which temporary typical myxedema can be produced by the administration and omission of iodine.<sup>9,10</sup>

Two-thirds of the treated cases were followed.

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### THE DISTINCTION BETWEEN METABOLIC AND NERVOUS SYMPTOMS IN THYROID DISORDER.

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WHEN one analyzes the syndrome presented by cases of exophthalmic goiter, the symptoms tend to form themselves into two groups, one of which is due to disorder of the metabolic processes of the body, the other the result of disordered nervous function. In the first group of symptoms may be listed increased basal metabolic

rate and weight loss. Associated with the increased metabolic rate and increased heat production, there appears symptomatic evidence of the compensatory effort of the body to dissipate heat as manifested by the hot, flushed skin and increased temperature of the body surface. In the second or nervous group are the nervousness, excitability and emotional instability, the tremor, sweating, tachycardia and palpitation.

It would seem that this is a reasonable division of the symptoms on a basis of function, although the arbitrary classification of some of the symptoms in one group or the other might be objected to with reason. Nervousness and emotional instability are certainly manifestations of a disturbed psyche. This might be explained as the result of increased metabolic activity of nerve cells; but the symptoms are common to many conditions unassociated with increased metabolic rate and, for this reason, it seems proper to classify them as primarily of a nervous nature. The tremor likewise might be accounted for from the standpoint of increased muscle-cell activity, but this is a symptom which also is frequent in conditions associated with normal metabolism. Moreover, tremor is induced in the normal individual by the injection of adrenalin which acts by stimulation of the sympathetic nervous system and it, therefore, seems a neurologic rather than a metabolic disturbance. Tachycardia is partly metabolic since increased bloodflow is necessary for increased oxygen supply of the tissues, but, like sweating, which may be an effort at heat dissipation, its intensity is strikingly influenced by emotional reactions and it reflects an imbalance of the autonomic nervous system in which the cardiac accelerators are overactive.

An attempt to classify the symptoms comprising the syndrome as metabolic and neurogenic may seem unnecessary and confusing, but in our own experience we are often impressed by the rather clean-cut way in which one or the other of these symptom groups dominate the clinical picture and by the variation in the relative intensity of the two groups.

In the typical case of exophthalmic goiter the nervous symptoms and the metabolic disturbance are, as a rule, equally intense and their intensity varies in equal ratio. There are conditions which simulate very closely the picture of thyroid toxemia as regards the nervous symptoms but in which the metabolic symptoms are lacking. For this reason, there are frequently referred to the thyroid clinic, as cases of hyperthyroidism, individuals suffering from conditions variously diagnosed as anxiety neurosis, shell shock, or neurocirculatory asthenia. These cases resemble in their nervous instability, their tachycardia, and in their tremor the true case of hyperthyroidism so closely that diagnosis must often be deferred until their metabolic rate has been determined, although they can often be differentiated clinically by the absence of any marked loss of weight and the absence of the hot and flushed skin aptly described as the

thyroid "glow." Many regard this type of case, in spite of the absence of demonstrable thyroid enlargement, as suffering from derangement of thyroid function—a perversion if not an excess of thyroid secretion. There seems to be no convincing evidence at present either to prove or disprove this view.

In two cases under our observation, both of whom had definite goiters, the nervous symptoms have so dominated the picture and have been so out of proportion to the metabolic rate, we have been in doubt as to whether they should be classified as goiterous individuals with a neurosis, or as goiterous individuals with thyroid toxemia.

**Case Reports.** CASE I.—The first of these cases (Chart I) was a girl, aged twenty-three years, admitted to St. Luke's Hospital in 1920 with an enlargement of the right thyroid lobe and complaining of nervousness, weakness and cardiac palpitation. She had a tremor but no exophthalmos. Her pulse over a period of three weeks ranged from 96 to 120. At this time, facilities for estimating her basal metabolic rate were not available. She was regarded as a case of thyroid toxemia and a right lobectomy was performed. Pathologically, the removed thyroid lobe was found to contain two colloid cysts with dense fibrous capsules surrounded by normal gland parenchyma and the pathologic diagnosis was returned of "colloid cyst in colloid goiter, no hyperplasia." Improvement in the nervous symptoms followed the operation for three months, when she was admitted to the Thyroid Clinic. At this time, she presented from the nervous standpoint the picture of a moderately severe thyroid toxemia. She complained of nervousness, sweating, cardiac palpitation and fatigue. She had a definite tremor but no exophthalmos or thyroid enlargement. She was under observation for nearly three years during which time five metabolic tests were made which ranged from +11 to +17 per cent. These may be regarded as normal. Throughout this period of observation her nervous instability continued with some variation in intensity. During this time, she was admitted to the hospital and operated upon for the removal of a suppurative appendix. A few days following the operation, she developed an acute psychosis with delusion and hallucinations. At this time, her condition did not suggest, except for her mental state, a thyroid crisis. This psychosis subsided in ten days and she returned to the clinic in the same condition as before operation.

Unfortunately, the relation of the micropathology to the clinical symptoms in thyroid disease is often not clear-cut, but the thyroid pathology in this patient's case was that of the type of goiter usually associated with local and not constitutional symptoms. The toxic goiter is, as a rule, characterized by cellular or acinar hyperplasia which was not present here. It would be idle to go into the merits of arguments for and against the idea that disturbed thyroid function was the basis of this patient's symptoms. She presented a picture of nervous instability which is not infrequently seen in young women, with and without goiters. To us, it seems more logical to classify her as a psychoneurotic who gained no permanent benefit, as far as her nervous symptoms were concerned, from the removal of a simple goiter. She represents the extreme of the not uncommon

CHART I.—ANALYSIS OF CASE I.

Date.	Mar. 4, 1921.	Mar. 18, 1921.	Apr. 8, 1921.	Apr. 22, 1921.	May 6, 1921.	June 9, 1921.	June 24, 1921.	July 23, 1921.	Aug. 5, 1921.	Sept. 3, 1921.	Oct. 15, 1921.	Nov. 12, 1921.	Nov. 25, 1921.	Dec. 16, 1921.	Sept. 21, 1922.	May 26, 1923.	June 2, 1923.	Dec. 29, 1923.
Nervousness	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Palpitation	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Sweating	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Tremor	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Weakness	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Pulse	116	110	120	132	122	128	117	130	128	114	112	122	120	120	140	132	118	108
Weight	133	129	125	124	119½	114	116	118	117	118	117	117	114	114	132	125	124	120
Basal metabolism	..	..	..	..	..	11	..	..	..	..	14	..	14	13	..	..	13	..

CHART II.—ANALYSIS OF CASE II.

Date.	Jan. 16, 1928.	Jan. 14, 1928.	Jan. 21, 1928.	Feb. 18, 1928.	Feb. 25, 1928.	Mar. 3, 1928.	Mar. 31, 1928.	Apr. 14, 1928.	Apr. 28, 1928.	May 5, 1928.	May 12, 1928.	May 26, 1928.	June 2, 1928.	June 9, 1928.	June 30, 1928.	July 14, 1928.	July 28, 1928.	Aug. 18, 1928.	Sept. 7, 1928.	Sept. 14, 1928.
Nervousness	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Palpitation	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Sweating	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Tremor	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Weakness	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Pulse	100	100	100	140	132	140	120	120	124	120	120	128	96	120	116	116	106	124	118	100
Weight	94	94	100	104	105	107	110	112	115	116	113	117	119	121	123	123	122	120	121	121
Basal metabolism	+18	+16	..	..	+15	..	..	..	+10	..	..	..	..	..	..	+13	..	..	..	+7

type of nervous girl with a goiter. This type is popularly diagnosed as being hyperthyroid, particularly if the diagnosis can be supported by reports from the laboratory of a few points elevation in the normal metabolic rate. How much, if any, disturbance of thyroid physiology has to do with their nervousness must be left to theory, practically surgical reduction of thyroid tissue should not be offered as a remedy for the nervous instability in the absence of definite metabolic disturbance.

This patient's chart is represented in the first of the illustrations. In these charts, symptoms are recorded according to their intensity as accurately as such symptoms can be in terms of +, ++, +++, +++++.

CASE II.—The second case (Chart II) is that of a young Hebrew, aged thirty-two years, who first came under observation in November, 1927. He dated the onset of his illness at the time of the influenza epidemic, nine years before, when his father, mother and one brother died in rapid succession of this disease. Since then, his health had not been good. He had become nervous and had lost much weight. His condition had apparently puzzled the physicians whom he had consulted and for a time he was suspected of suffering from incipient tuberculosis. On his first appearance at the Thyroid Clinic, it seemed obvious that he presented the usual picture of Grave's disease of moderately severe type. He was extremely nervous, had a marked tachycardia and tremor and sweated profusely. His eyes were of the staring type, which suggest exophthalmos in a thyroid suspect, but which are often seen in normal individuals. There was a definite smooth goiter with moderate enlargement of both thyroid lobes and isthmus. Upon further examination, the predominance of the nervous elements of his clinical picture became evident. One of his prominent symptoms was his phobia for closed spaces. He preferred the open ward to the quiet room usually allotted to thyroid patients. His skin was cold rather than hot and flushed, as is usual in cases of Grave's disease. Two basal metabolic readings were obtained, one of +18 and one of +16 eight days later. There developed between the patient's medical and surgical attendants different points of view. The surgeon felt that nervousness, tremor and tachycardia in the presence of a goiter were sufficient indications for the surgical reduction of thyroid tissue and was rather intolerant of any explanation, other than a thyrogenic one, for the patient's condition.

The internist expressed himself as being doubtful of the benefit which would come to the patient, as regards his nervous instability, from thyroidectomy. He preferred to consider the nervous manifestations as purely nervous in character or as residual symptoms following a thyroid toxemia in the past and advised against an operation. The patient needless to say accepted the advice which he preferred, and continued under observation without operation. He was hospitalized for a period of six weeks and since then has been occupied with part-time work. His treatment has been purely symptomatic. His subsequent course is represented by Chart II. It will be seen that over a period of nine months he has gained 27 pounds in weight, that his metabolic rate has been within normal limits and that his nervous instability has become less intense. While he has made a marked gain in weight and strength he remains as yet nervously quite unstable. In this individual with a goiter, the nervous symptoms seen in exophthalmic goiter were pronounced but while under our observation he presented no definite symptoms of increased metabolism.

CHART III.—ANALYSIS OF CASE III.

Date.	Apr. 16, 1927.	May 7, 1927.	May 21, 1927.	June 4, 1927.	July 23, 1927.	Aug. 6, 1927.	Sept. 10, 1927.	Oct. 22, 1927.	Nov. 5, 1927.	Nov. 26, 1927.	Dec. 17, 1927.	Jan. 28, 1928.	Feb. 18, 1928.	Mar. 24, 1928.	Mar. 31, 1928.	May 12, 1928.	May 19, 1928.	June 2, 1928.	June 30, 1928.	Sept. 29, 1928.
Nervousness	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Palpitation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sweating	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tremor	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Weakness	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pulse	124	126	118	104	104	120	116	112	124	124	96	100	116	128	116	134	120	120	124	96
Weight	133	132	134	142	137	137	139	137	140	140	139	138	133	137	139	137	135	134	141	138
Basal metabolism	+43	.	.	+31	.	+25	.	.	+31	.	.	.	+50	+35	.	.	.	.	.	+49

CHART IV.—ANALYSIS OF CASE IV.

Date.	Sept. 10, 1926.	Sept. 29, 1926.	Nov. 13, 1926.	Jan. 3, 1927.	Jan. 15, 1927.	Feb. 19, 1927.	Apr. 23, 1927.	May 28, 1927.	Aug. 13, 1927.	Oct. 1, 1927.	Oct. 22, 1927.	Nov. 5, 1927.	Dec. 6, 1927.	Jan. 14, 1928.	Mar. 31, 1928.	June 15, 1928.	July 28, 1928.	Sept. 29, 1928.	Nov. 10, 1928.	
Nervousness	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Palpitation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sweating	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tremor	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Weakness	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pulse	100	80	88	72	68	72	88	104	90	84	74	84	80	80	84	88	92	82	82	82
Weight	130	130	139	145	145	147	144	142	147	154	154	153	152	154	153	145	149	149	144	144
Basal metabolism	+40	+21	.	.	+12	.	.	.	+21	.	+19	.	.	+12	.	.	.	+21	+21	+19

The varying relationship between the metabolic and nervous factors in the symptom complex is an interesting study. In some of our cases, we have seen the nervous manifestations subside to a great degree while the metabolic rate continued high, but more frequently the nervous manifestations remain severe in spite of a comparatively low metabolic rate.

The former of these two types is represented by Chart III.

CASE III.—This is a case of a colored woman with exophthalmos and a rather large goiter. She presented on admission the nervous symptoms of moderate intensity and a basal metabolic rate of +43. She was referred for treatment to the radiotherapeutic department. As may be seen from her chart, there was marked symptomatic improvement in the course of two months but despite her lack of present subjective complaint her basal metabolic rate remains high.

CASE IV.—The opposite is represented by Chart IV which is that of a woman, aged forty-two years, admitted to the hospital with a goiter, exophthalmos, nervousness and cardiac palpitation. Her metabolic rate was +40. She was operated upon September 14, 1926, and pathologically the gland was largely colloid in character but had definite areas of hyperplasia. After operation, her metabolic rate dropped and she gained weight, but, as will be seen from her chart, the nervous symptoms have continued.

CASE V.—The development of metabolic derangement in a patient with long-standing nervous instability is illustrated by Chart V. This patient, a woman aged forty-three years, first came under observation on the surgical service, in 1922, complaining of pain on defecation. Associated with this discomfort, she complained of nervousness and fatigue. A proctoscopic examination was made under a general anesthetic, no lesion was demonstrated, the anal sphincter was dilated, and she was later discharged with a diagnosis of psychasthenia. Six months later, she came under observation again, complaining chiefly of indefinite pain in the lower right abdomen. She felt nervous and tremulous, suffered from cardiac palpitation, perspired easily and had lost 12 pounds in the preceding year. While the symptom for which she sought relief was the abdominal discomfort, her nervous symptoms were prominent and suggested hyperthyroidism. She was admitted to the hospital for investigation. Gastrointestinal investigations failed to reveal any organic lesion. Her basal metabolic rate was +17. Although her symptoms strongly suggested hyperthyroidism, this metabolic rate and the absence of demonstrable thyroid enlargement led us to discharge her with a diagnosis of psychoneurosis. She returned three months later, October 16, 1923, with the same nervous symptoms. Examination of her thyroid at this time revealed a globular swelling in the thyroid isthmus. Her basal metabolism was +35. A diagnosis of adenomatous goiter with hyperthyroidism was then made. After rest in bed, she was operated upon and the isthmus of the thyroid which seemed to contain an adenoma was removed. Later, the section of this tissue showed it to be hyperplastic and not adenomatous in type. She remained under our observation for the next four months during which time she showed marked improvement, although the nervousness and palpitation persisted in a milder degree. Her basal metabolic rate during this time was normal and she gained considerably in weight. She then passed out of our direct observation but we have learned that there have since been several periods when, after times of emotional or physical stress, the nervous symptoms have returned with intensity, although she has reached a weight of 175 pounds (about 30 pounds more than at operation) and her metabolic rate on several tests has never been higher than +15.



CHART V.—ANALYSIS OF CASE V.

Date.	July 4, 1923.	July 13, 1923.	July 21, 1923.	Oct. 16, 1923.	Oct. 23, 1923.	Nov. 16, 1923.	Dec. 11, 1923.	Jan. 22, 1924.	Feb. 26, 1924.	Apr. 24, 1924.	Oct. 16, 1924.
Nervousness	+	+	+	+	+	+	+	+	+	+	+
Palpitation	+	+	+	+	+	+	+	+	+	+	+
Sweating	+	+	+	+	+	+	+	+	+	+	+
Tremor	+	+	+	+	+	+	+	+	+	+	+
Weakness	+	+	+	+	+	+	+	+	+	+	+
Pulse	108	110	120	100	100	88	92	159	68	88	72
Weight	136	131	...	141	141	141	148	159	163	166	163
Basal metabolism	+17	...	...	+35	+25	+9	+6	+4	-3	-5	-11

CHART VI.—ANALYSIS OF CASE VI.

Date.	Apr. 10, 1921.	May 28, 1926.	June 10, 1926.	June 17, 1926.	June 28, 1926.	July 10, 1926.	July 26, 1926.	Sept. 4, 1926.	Sept. 8, 1926.	Sept. 13, 1926.	Oct. 1, 1926.	Nov. 15, 1927.
Nervousness	...	...	+	+	+	+	+	+	+	+	+	+
Palpitation	...	...	+	+	+	+	+	+	+	+	+	+
Sweating	...	...	+	+	+	+	+	+	+	+	+	+
Tremor	...	...	+	+	+	+	+	+	+	+	+	+
Weakness	...	...	+	+	+	+	+	+	+	+	+	+
Pulse	84	90	100	100	100	120	112	120	120	110	88	88
Weight	130	135	131	...	124	121	113	115	108	109	111	139
Basal metabolism	-4	...	+17	...	+19	+21	+24	+41	+44	+30	+19	-5

The relation of the nervous symptoms in this case to the function of the thyroid is a subject for considerable conjecture. Some would interpret the entire picture in terms of thyroid oversecretion or faulty secretion and perhaps advise a subtotal thyroid resection to obtain complete restitution to health. To us, it seems more probable that the patient is a psychoneurotic who developed a thyroid toxemia from which she was relieved by rather conservative surgery. Her case would tend to support the theory that the underlying cause of Grave's disease is a nervous disorder which stimulates the thyroid to oversecretion.

The opportunity is not often offered to study the development of the exophthalmic syndrome from its onset. It is recognized that exophthalmic goiter develops with great frequency in individuals who seem always to have been of a nervously unstable type, but this is not always the case. We have had the opportunity in one case to watch the development of the syndrome in a young woman who, until the onset of her illness, had seemed of an unusually stable nervous type.

CASE VI.—In this case, the nervous symptoms seemed to antedate the rise in metabolism or at least had become quite marked before the metabolic rate became high enough to be of diagnostic importance. This patient, three months before the onset of her illness, had had a febrile respiratory attack diagnosed as influenza. Following this she had suffered for six weeks from headaches. She recovered from these and one night after retiring she began abruptly to have cardiac palpitation. After this she became increasingly nervous. Five years previously her metabolism had been found to be  $-4$ . Two weeks after the onset of her palpitation, her metabolic rate was found to be  $+17$  and rose gradually in the next six weeks to  $+24$  by which time her nervous symptoms had become intense and a definite thyroid enlargement had appeared. Later her metabolic rate rose to  $+44$  and she was admitted to the hospital, where, after preparatory treatment with Lugol's solution, a subtotal thyroidectomy was done. The gland tissue was found to be hyperplastic in character.

In the early weeks of observation there was some doubt as to the diagnosis of this patient's condition. She presented the nervous symptoms frankly enough but it was not considered that her metabolic rate was definitely elevated. The first reading of  $+17$  was above the 10 per cent variation usually given as normal but we do not feel that in nervous individuals a reading under  $+20$  is to be relied upon, either as a diagnostic or therapeutic guide. This patient received prompt relief of both metabolic and nervous symptoms from operation. She represents the type of nervously stable individual in whom the expectation of prompt and thorough relief from operation is much better than in the constitutionally unstable type.

**Summary.** The cases reported here emphasize the distinction between symptoms resulting from disturbance of the metabolic and those resulting from disturbance of the nervous mechanism of the body. The rôle of the thyroid in the production of metabolic disorder is obvious. The nature of the nervous disorder and of the agency which induces it is obscure. The nervous disorder which, for the most part, represents a disturbance of the autonomic nervous

system may be either the cause or the result of thyroid disturbance. There is no reason to believe that disorder of the autonomic system may not result from other agencies than faulty thyroid secretion. The recognition of this fact is important because of the frequency with which a clinical picture made up of nervousness, tremor and tachycardia presents itself. A diagnosis of hyperthyroidism, when these symptoms are present without definite increase in metabolism, should be made with a great deal of reluctance. This is especially important as regards the nervous adolescent girl with a goiter who is often diagnosed and sometimes operated upon for Graves' disease if minor elevation in metabolism is present.

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### EXOPHTHALMOS FOLLOWING OPERATION FOR THE RELIEF OF HYPERTHYROIDISM.\*

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THE etiology of exophthalmos in diseases of the thyroid gland is unknown. Our ignorance of its mechanism is attested by the numerous hypotheses advanced, none of which, apparently, has been found entirely convincing. As to its significance, however, there has been less dispute. Described as one of the cardinal symptoms of hyperthyroidism, it has given name to the so-called "primary" form of the disease, and attempt has been made to divide thyrotoxic states into two groups, largely on the presence or absence of ocular symptoms. The appearance of exophthalmos has usually been considered indicative of high-grade, long-standing thyrotoxicosis. Immediately after the operation for toxic goiter, with the exacerbation of the other symptoms, there is often a transient increase in the prominence of the eyes. Following the surgical cure of the disease, the bulging of the eyeballs is expected to recede, and in milder cases, to disappear entirely. Often, the ocular changes are very slow to improve, gradual recession sometimes taking place many months after all other manifestations of the disease have disappeared; and in severe cases, the exophthalmos may persist permanently.

In the past year or so we have several times observed what appears to be a paradoxical development of exophthalmos. In a total of eight cases of hyperthyroidism, in which the process has been cured by thyroidectomy, exophthalmos has developed after the operation. In every case, the metabolic rate has been brought

(\* Read before the Chicago Society of Internal Medicine, February 25, 1929.)

to normal or below by the operation, and the exophthalmos has not been accompanied by any other manifestation of hyperthyroidism. In some of these patients there was no exophthalmos whatsoever at the time of operation. In others, in whom a suggestion of eye change had been noted, the protrusion increased noticeably after the thyroidectomy. In every case, the change was sufficiently marked to attract the attention of the patients or their friends. In one instance, the exophthalmos became so extreme, the upper lid retracted behind the eyeball, producing the effect of a luxation of the orb. Usually the increased prominence of the eyes was accompanied by conjunctivitis, lacrymation, and in several instances, by chemosis and edema of the lids. One case was complicated by the development of a retinitis pigmentosa, which appeared simultaneously with



Exophthalmos following operation for the relief of hyperthyroidism.

the exophthalmos. In five of the cases, the exophthalmos was frankly bilateral, in the other three it was limited chiefly to one eye. The interval between the operation and the time the increased prominence of the globes was noted ranged from three to twelve months. It has persisted to date from eight months in the earliest case to three months in the latest, without improvement in any instance. Six of the patients in the series have been operated upon by Dr. H. M. Richter; the seventh, seen through the courtesy of Dr. C. A. Elliot, was operated upon by Dr. Crile in Cleveland, and the eighth is a patient in the thyroid clinic of the Michael Reese Dispensary, who had been operated upon by the thyroid group of the Michael Reese Hospital.

**Case Reports.**—CASE I. Patient J. L., male, aged fifty-three years, complained of symptoms of moderately severe hyperthyroidism of but six months' duration. His basal metabolic rate fell from +62 to +45 on Lugol's solution, and on December 22, 1927, subtotal thyroidectomy was done. The eyes had always been rather prominent, but had not become more so with the present illness. After leaving the hospital, the patient's condition improved rapidly, but symptoms of hypothyroidism soon appeared and thyroid substance in 2-grain doses was administered. When seen March 20, 1928, the metabolism was -20 and there were mild symptoms of thyroid insufficiency. At that time, it was noted that the exophthalmos was more marked than ever before. There was considerable conjunctivitis and chemosis of the cornea, and the patient complained of irritation and profuse lacrymation. Thyroid substance in doses of 5 grains daily brought the basal metabolic rate up to +7, and the symptoms of hypothyroidism rapidly and completely disappeared. The condition of the eyes, however, remained unchanged, and the patient complained of diplopia. When seen eight months after the operation (see illus.), he again had symptoms of hypothyroidism, and the metabolism was -18. The exophthalmos had remained about the same, although much of the inflammation had subsided. He still complained of lacrymation. He was given thyroid, grains 3 daily, and Lugol's solution, minims 10 three times a day. Two weeks later, there was improvement in the hypothyroid symptoms, but no appreciable change in the eyes.

CASE II.—Patient A. T., male, aged fifty years, presented symptoms of high-grade toxic goiter, of two years' duration, with basal metabolic rate of +66. No change in the appearance of the eyes had been noted by the patient or his wife, although record of the physical examination states there was "definite exophthalmos." After the usual preliminary treatment with iodine, thyroidectomy was done on December 13, 1927. A "moderately large, diffusely hyperplastic thyroid, with one rather large adenoma in the lower pole of the left lobe" was removed, and the patient made a rapid and uneventful recovery. On January 6, 1928, he felt well, but basal rate was -15, and there were symptoms suggestive of mild hypothyroidism. Thyroid, in doses of 1 grain a day, was administered. April 13, he complained of eyes "watering," especially when out of doors, and he stated that he could not focus on anything very long. Conjunctivitis was noted, but no other change. Basal rate at that time was -32.6 and pulse 58. Thyroid was increased to 2 grains daily. One month later he complained of exudate from the eyes, and stated that there had been a definite increase in the prominence of the eyeballs since the operation. At that time there was high-grade exophthalmos, with conjunctivitis, edema of the lids and slight chemosis. August 20, 1928, nine months after the operation, patient had definite symptoms of myxedema, with basal metabolism of -35. The eyes were still very prominent (patient thought more so than at the previous visit) and he was troubled with swelling of the lids and constant lacrymation. Thyroid, 5 grains daily, and Lugol's solution, 10 minims three times a day were prescribed. Two weeks later, the hypothyroid symptoms were partly relieved, but the condition of the eyes remained unchanged. Exophthalmometric readings (Dr. Harry Gradle) were: April 13, 1928, 22/21; June 9, 1928, 24/23.

CASE III.—Patient R. M., male, aged forty years, complained of rather acute symptoms of hyperthyroidism, of only about two months' duration, with basal metabolic rate of +48. No change in the eyes had been noted, and the record of physical findings states there was "no exophthalmos, but a suggestive von Graefe was present." Preoperative treatment with

iodin was followed by a subtotal thyroidectomy on March 17, 1928. Convalescence was entirely without incident, and when patient was seen March 30, his basal rate was +2 and he expressed himself as "feeling fine in every respect." He returned to his home in another city and was not seen again until July 7, when he reported, greatly alarmed because of the condition of his eyes. He stated that they were bulging, a condition which had developed since the operation, and that they were inflamed and teared constantly. Examination revealed definite exophthalmos, with marked swelling of upper and lower lids. There was high-grade conjunctivitis and lachrymation. Basal metabolism was -15, pulse 66.

CASE IV.—Mrs. A. F., aged forty-four years, was referred for surgery because of moderately severe hyperthyroidism of the "primary" type, of about one year's duration. Basal metabolic rate before treatment was started was +36. There was no exophthalmos at that time, nor were any of the lid symptoms demonstrated. Thyroidectomy was done on April 8, 1927. Six weeks later she began to show evidences of hypothyroidism, and basal rate was -17. Symptoms subsided with thyroid medication. Since then, the patient has been under the care of Dr. C. A. Elliot. His record of October 14, 1927, states "No prominence of globes, freely movable in every direction. No von Graefe's sign." One year after the operation, the left eye was seen to be slightly wider open than the right. At that time, the patient was receiving 6 grains of thyroid daily, and her metabolism was -10. She was given Lugol's solution, 3 drops daily, and ten days later the widening of the palpebral fissure had disappeared. The iodine was discontinued, but was started again on May 2, when the prominence of the left eye reappeared. The unilateral exophthalmos has persisted to date, in spite of continuance of iodine medication.

CASE V.—Mrs. E. L., aged fifty-three years, was operated upon in September, 1926, because of hyperthyroidism. She consulted Dr. Elliot in February, 1928, at which time her basal metabolic rate was -20. She complained of exophthalmos, and stated there had been none before the operation. She had been taking thyroid from November to January but had not received any for the month preceding the examination because it made her nervous. No iodine had been prescribed since the operation. At the time of examination, there was "definite stare and lid lag." She was given Lugol's solution, 3 drops daily, and a week later, the eyes seemed less prominent. When seen the following week, the patient was fatigued, and definite exophthalmos was noted. On April 9, the condition of the eyes was unchanged and the basal rate was -27. The iodine was discontinued and thyroid administered. Prominence of the left eye has persisted and is more marked when patient is fatigued or nervous. The latest metabolic rate was -15.

CASE VI.—B. G., male, aged thirty-seven years, complained of hyperthyroid symptoms of five months' duration, with initial basal metabolic rate of +72. "Slight exophthalmos" was noted at the time of operation, although neither the patient nor his family were aware of any change in the appearance of the eyes. Thyroidectomy was done on December 29, 1927, after three weeks preoperative treatment with iodine. On February 1, 1928, he was examined in the eye dispensary because of pain and tearing of the eyes, and a "salt and pepper fundus" was found. The symptoms progressed in severity, and on July 17, 1928, beginning exophthalmos was noted. Basal metabolism was +8, and there were symptoms of neither hypothyroidism nor hyperthyroidism. Since then, the prominence of the eyes has increased, and the patient has suffered from photophobia, lacryma-

tion, conjunctivitis and marked edema of the lids. There has been a rapidly progressing loss of vision and the fundus changes have led to the diagnosis of retinitis pigmentosa.

CASE VII.—Miss B. M., aged twenty-nine years, had mild symptoms of thyrotoxicosis, with basal rate about  $+25$ . Lugol's solution relieved the symptoms and brought the metabolism down to  $+1$ . After two and a half months of iodine treatment, however, the symptoms began to recur, and thyroidectomy was advised in spite of the low metabolic rate. The eyes were normal, there was neither lid lag nor widening of the palpebral fissures. Following the operation, the rate dropped to  $-18$ , and although there were no hypothyroid symptoms, thyroid in doses of 2 grains daily was administered for a period of two months. One month after stopping the thyroid, the patient noticed enlargement of the eyes, especially affecting the left one. There were no symptoms of hyperthyroidism and none of myxedema. Six months after the operation she was in good condition, with basal metabolic rate of  $-14.4$  and free from symptoms. The right eye was normal in size, the lid followed well and ocular movements were unrestricted. The left eye was markedly exophthalmic and there was lagging of the upper lid. There was no conjunctivitis and no edema of the lids or cornea, and the patient stated she was rarely conscious of inflammation of the eyes or of swelling of the lids. Thyroid and iodine were prescribed.

CASE VIII.—Miss S. C., aged nineteen years, was operated upon September 29, 1927, for moderately severe hyperthyroidism. Exophthalmos was noted before operation but was not sufficiently marked to attract the notice of the patient or her mother. Soon after her discharge from the hospital, the patient began to be aware of a growing prominence of the eyeballs, affecting both eyes, but the left more than the right. Six months after the operation her basal rate was  $-8$ , and she was entirely free from symptoms, except for puffiness of the eyelids. The eyes continued to enlarge, and she was aware of a feeling of "tiredness and strain" in the eyes. One year after the thyroidectomy, there was high-grade bilateral exophthalmos, the left eye protruding more than the right. On November 15, 1928, dust was blown into her eyes and she rubbed them lightly. The upper lid of the left eye retracted behind the eyeball, producing the effect of luxation of the orb. The patient was greatly frightened, but was able to bring the lid over the bulb without assistance. Her metabolic rate one week later was  $-19$ .

In the 8 cases here reported, in which thyroidectomy was done because of toxic goiter, exophthalmos developed or became more pronounced following the operation. In every instance, the basal metabolic rate was brought to normal or below by the operation, and in none was there clinical evidence of persisting or recurring hyperthyroidism. Three of the patients had very slight exophthalmos at the time of operation, and 2 others showed lagging of the upper lid. In all, the symptoms increased greatly after the thyroidectomy, the exophthalmos in one case becoming so extreme as to permit the upper lid to retract behind the eyeball. Four of the 8 had evidences of hypothyroidism, and 3 others had basal rates from  $-15$  to  $-19$ , although all 3 were from hypothyroid symptoms. Five of the group had received thyroid substance before the increased exophthalmos was noticed, but in several of these the thyroid treatment had been stopped for one to two months before the eye changes appeared. It is

significant that none had received iodine before the onset of the exophthalmos, except in the preoperative period and during the first few days after operation. Once the prominence of the eyes had developed, it was neither improved nor made worse by the administration or discontinuance of thyroid substance. In Case I, the basal metabolic rate was brought up from  $-20$  to  $+7$  with thyroid, then allowed to drop back to  $-18$  without in any way affecting the condition of the eyes. In 2 of the patients, small amounts of iodine caused a temporary recession of the exophthalmos, but when it reappeared, further iodine medication was without effect. Recently, several of the group have been given full doses of iodine, together with sufficient thyroid to correct any existing hypothyroidism. The period of observation under this régime has been too short to permit definite statement, but as yet, no appreciable improvement of the ocular symptoms has occurred.

It is interesting to note that despite the great preponderance of females treated for hyperthyroidism, as compared with males, 4 of the 8 cases here reported were in men. The ages of the patients in the series ranged from nineteen to fifty-three years. In the 7 cases in which the entire case histories are available, the hyperthyroidism was apparently of the "primary" type. The gland removed in each case was diffusely hyperplastic, more or less involuted by the preoperative use of iodine. In Case II, there was in addition, a discrete adenoma in the lower pole of the left thyroid lobe.

While no definite explanation is offered for this phenomenon, several important questions are raised. The observation of so many cases within so short a period of time makes it improbable that we are dealing with an accidental occurrence. The rapidity with which successive instances appeared after the first outstanding case was seen, suggests that others will be found, once they are looked for. It is to be emphasized that the eye changes occurred in patients completely cured of the manifestations of hyperthyroidism, with metabolic rates normal or below, and sometimes accompanying frank symptoms of hypothyroidism. In fact, the almost regular association of subnormal basal rates with this paradoxical exophthalmos, suggests a possible relationship between the eye change and thyroid insufficiency. Obviously, then, the exophthalmos cannot be considered an indication of persisting thyroid intoxication in the sense in which the latter condition is usually recognized.

In his Beaumont lecture of 1925, Plummer<sup>1</sup> states in support of his "two-product theory" of exophthalmic goiter, that following extensive resection of the thyroid, the greatly stimulated remnant of gland tissue should deliver a subnormal amount of thyroxine, and some of the abnormal agent. In accord with this is the observation that in mild recurrent cases, the nervous phenomena and not infrequently progressive exophthalmos are the outstanding features, although the basal metabolism is relatively low. He cites one case,



which was later described in a separate case report by Haines,<sup>2</sup> in which such manifestations were present with a basal rate of  $-14$ . When iodine was given, the rate dropped to  $-28$ , the symptoms disappeared, and the picture of myxedema supervened. By the simultaneous administration of iodine and thyroid, the patient was maintained free from either group of symptoms. While in our cases, the regular accompaniment of nervous phenomena with the exophthalmos was not observed, this explanation for the eye changes seems plausible. In line with this is the transient improvement obtained in 2 of the patients by the use of iodine, and the fact that although further use of Lugol's solution was without effect in correcting the exophthalmos, these 2 cases showed the slightest changes of any in the series. As stated, the combined use of Lugol's solution and thyroid is being tried in several additional patients, although thus far no striking improvement has been observed.

Opposed to Plummer's theory, are the results of Kunde's<sup>3</sup> experiments with artificial hyperthyroidism. She found that all of the symptoms of exophthalmic goiter could be reproduced in laboratory animals by feeding thyroid or injecting crystalline thyroxine. Exophthalmos was not produced in the dog, but could be caused at will in the rabbit without the aid of any secondary product. It is interesting, though, that in the normal rabbit, excessive doses of thyroid produced only mild exophthalmos; while rabbits rendered myxedematous by early thyroidectomy, developed very marked proptosis. This latter condition is similar to that which prevails in several of our patients.

Attention should be called to the frequency with which conjunctivitis, edema of the lids, chemosis of the cornea, and even more serious disturbances accompanied the exophthalmos in the cases here reported. While such phenomena are seen occasionally with the exophthalmos of hyperthyroidism, they are extremely uncommon. In an article on "Orbital Edema in Exophthalmic Goiter," Thompson,<sup>4</sup> reports 3 cases in which acute edema of the orbit occurred, causing serious disturbances, even to loss of both eyes in one instance. It is significant that all 3 patients had been operated upon, partial thyroidectomy having been done in 2 cases, and polar ligation in the third. Unfortunately, the report does not state definitely whether there was persistence of the hyperthyroidism or not, although some of the symptoms mentioned suggest that the thyrotoxic condition had not been completely relieved. In these 3 cases, edema of the lids, chemosis, conjunctivitis and sloughing of the cornea suggested what, in a milder form, was characteristic of our cases. These symptoms, Thompson ascribes to an edema of the retrobulbar tissues, and it is altogether possible that such a factor may have been active in the cases here described.

**Summary.** Eight cases are reported in which thyroidectomy for the relief of hyperthyroidism was followed by the development of

exophthalmos. If some exophthalmos was present at the time of operation, it increased materially afterward. In every case the patients were completely relieved of their symptoms of hyperthyroidism, and the basal metabolic rate was brought to normal or below by the surgical removal of the gland. In three of the patients the eye change was limited to one eye, in the remainder it was bilateral. Conjunctivitis, chemosis and edema of the lids frequently accompanied the exophthalmos. The postoperative exophthalmos developed with a falling basal metabolic rate, was associated in most instances with subnormal metabolism and sometimes with frank myxedema, and was not accompanied by any other symptom of hyperthyroidism. Thyroid medication or the withholding of it seemed to have no effect on the ocular changes. No definite explanation is here offered for this apparently paradoxical phenomenon though pertinent observations are discussed.

Since this paper was submitted for publication, three additional patients have been observed in the service of Dr. H. M. Richter, who have developed increased exophthalmos following operation for the relief of hyperthyroidism. They present essentially the same characteristics as those described above.

NOTE.—I am greatly indebted to Dr. H. M. Richter for the privilege of using his material for this report.

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#### ACUTE THYROIDITIS.

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WHILE acute thyroiditis is ordinarily considered a rare disease, there appears to be conflicting evidence as to its frequency. It has been observed but twice on the service of Dr. H. M. Richter in a series of over 2000 goiter patients, 1000 of whom have been subjected to operation. It was encountered three times in over 3000 goiter operations at the Lahey Clinic.<sup>7</sup> I have, however, been able to collect 6 cases from the Cook County Hospital from 1921 to 1928 (where the amount of goiter material is comparatively small), and

Hagenbuch<sup>17</sup> found 43 cases among 45,953 medical and surgical admissions to the Basle Clinic during a ten-year period.

As early as the eighteenth century a number of descriptions of purulent and nonpurulent thyroiditis were given by Carron, Walter, Hadenus, Conradi and Bischof.<sup>6</sup> Conradi in 1824 and Bauchet in 1856, stated that the nonsuppurative type of thyroiditis was the primary stage of the purulent type. In 1878, Kocher stated that all inflammations of the thyroid were secondary to other foci and the correctness of such views was demonstrated bacteriologically by Tavel fourteen years later (1892). In 1895, Mygind, dividing thyroiditis in two classes, the simple and the suppurative, claimed that the former was in many instances a distinct disease entity. Ewald and von Eiselsberg disclaimed this, but De Quervain shared Mygind's view. Crotti<sup>6</sup> feels that a bacterial nonpurulent thyroiditis is only a phase of a process whose last act is suppuration. This suppurative stage may or may not be reached and we have no means of knowing what course a given thyroiditis will take. The determining factors are the virulence of the microorganism and the defense mechanism of the body. It is well known, however, that certain types of thyroiditis do not suppurate, for example, that occurring in scarlet fever, measles, parotitis, malaria and acute rheumatic fever.

**Etiology.**—Acute thyroid inflammation has been found at every stage in life. Demme<sup>6</sup> saw a congenital strumitis in a newborn babe; Burhan's<sup>1</sup> patient was seventy-seven years of age. It occurs most commonly, however, between the ages of twenty and forty years, and in women more often than in men. Of Robertson's<sup>23</sup> 96 cases, 52 were women; Burhans<sup>1</sup> found in 67 cases, 47 women and 20 men. Careful study of the available literature reveals the striking fact that acute thyroiditis nearly always follows in the wake of some acute infectious process, and in the majority of cases this infection originates in the upper or lower respiratory tract. Of Hagenbuch's<sup>17</sup> 43 cases, 8 followed influenza, 3 followed pleurisy, 6 occurred after Vincent's angina, and one followed a tooth extraction. In 9 other cases, the pneumococcus was the offending organism. Beilby<sup>3</sup> reported 3 cases of acute thyroiditis, all of which were associated with respiratory tract infection. Of Edward's<sup>12</sup> 4 cases, such infection was clearly demonstrable in 3. Clute and Smith<sup>7</sup> saw a case secondary to influenza; Greenburg's<sup>15</sup> case followed repeated attacks of sore throat, and in Bullowa's<sup>2</sup> case, chest injury and tonsillitis preceded the acute thyroid inflammation. The latter has also occurred after tonsillectomy<sup>13</sup> and laryngeal chondritis and perichondritis.<sup>4,24</sup> In 3 of the 8 cases forming the basis of this report, the respiratory tract lodged the primary focus of infection.

There are, however, other sources of thyroid inflammation. Tourneaux,<sup>27</sup> Bigger and Scribner<sup>5</sup> and Sabrazes<sup>25</sup> have recorded cases following typhoid fever; the latter collected 16 other cases of

typhoid thyroiditis from the literature. Within recent years, the French have described several cases due to infection with the paratyphoid A and B bacilli.<sup>21,8,11</sup> Seven cases occurring during pregnancy<sup>16</sup> are recorded. Acute thyroiditis has also followed puerperal fever,<sup>9,14,16</sup> meningitis,<sup>21</sup> septicemia,<sup>7,10</sup> erysipelas<sup>28</sup> and urinary tract infection.<sup>26</sup> Janney<sup>19</sup> states that in children it may occur secondary to measles, mumps, diphtheria, scarlet fever and malaria; according to Osler,<sup>22</sup> the lesion may occur in the course of smallpox, pneumonia and rheumatism. It is interesting to note that one of our cases followed an acute biliary-tract infection. Finally, it is stated that in Brazil a variety of trypanosomiasis caused by the *Schizotrypanum cruzi* (Chagas) is accompanied by acute thyroiditis.

**Symptoms.**—The symptoms are those produced by any acute inflammatory process, modified somewhat by the anatomic position of the gland.

Of interest are the symptoms of hyperthyroidism that may develop with the acute infection. It was noted seven times in the series recorded by Burhans. It has also been noted by Greenburg,<sup>15</sup> Funk,<sup>13</sup> Klose<sup>20</sup> and Hagenbuch.<sup>17</sup> These symptoms disappear with subsidence of the infection, but may be followed later by symptoms of hypothyroidism, due to destruction of the parenchymatous elements. Hallberg<sup>18</sup> obtained accurate data in 8 cases of non-suppurative thyroiditis from the Mayo Clinic, and found that in 7 of these, myxedema developed. One of our own cases (D. M.), began to show symptoms of hypothyroidism five months after the thyroid infection.

**Prognosis.**—The prognosis in nonsuppurative lesions is good, the disease being apparently self-limited with rapid and complete healing. In the suppurative cases, the prognosis for recovery is good if proper treatment is provided early. In these cases convalescence is long, chiefly because of complications. The latter may include rupture of an abscess into some neighboring viscus, edema of the larynx, bronchopneumonia, chondritis and perichondritis of the laryngeal cartilages. Recurrences have been reported. Hagenbuch<sup>17</sup> reported 2 deaths in 47 cases (4 per cent). In Robertson's<sup>23</sup> series of 96 cases, 2 of 54 nonsuppurative cases died and 9 of the 41 purulent cases died. Of Burhan's<sup>1</sup> 67 cases, 11 died.

**Treatment.**—For the simple inflammatory lesions of the thyroid, symptomatic treatment suffices. In specific types of thyroiditis, such as those due to typhoid bacillus or the meningococcus, the administration of specific curative measures, typhoid vaccine, anti-meningococcus serum, have been reported of value,<sup>21,25</sup> probably on the basis of a foreign-protein reaction. In the suppurative type, prompt incision and drainage are indicated. The usual approach to the thyroid, by way of a transverse incision, is advocated. If a lobe is encountered that contains numerous small abscesses, subtotal hemithyroidectomy should be done (Clute and Smith).

**Case Reports.** The 8 cases forming the basis of this report are presented briefly below:

**CASE I.**—Mrs. D. M., aged twenty-four years, white, presented herself complaining of abdominal pain of one month's duration, and pain in the neck, of twenty-four hours' duration. A goiter had been present for five years. For the preceding two years she had been having digestive disturbances suggestive of gall-tract disease. Five weeks before admission, a severe biliary colic occurred, followed in a few days by jaundice, which lasted for about a week. Abdominal pain was present intermittently for the ensuing month. The day before admission she began to complain of pain and stiffness of the neck, had severe chills, and felt feverish. When first seen the temperature was 103° F., the pulse rate 100, and the respirations 22 per minute. The general appearance was that of an acutely ill person. Movements of the neck were restricted in all directions. There was exquisite tenderness over the thyroid, most marked over the left lobe, which appeared to be somewhat enlarged. There was no evidence of fluctuation. On palliative treatment, the process subsided and in two weeks she was discharged. Three weeks later, her basal metabolic rate was -28, the basal pulse 45, and her weight 129 pounds. There were no subjective symptoms. One month later, a second metabolic rate was -18, basal pulse 52, and her weight had increase 2 pounds. A third metabolic rate three months later was -17, pulse 56, and her weight had increased 10 pounds. A large firm left-sided adenoma was now palpable, the right lobe being smaller and softer. She was complaining at this time of symptoms evidently of hypothyroidism, and was accordingly placed on desiccated thyroid substance.

**CASE II.**—Mrs. P. O., aged twenty-five years, white, stated that she had been unaware of any thyroid enlargement until five days before admission, when she noticed a painful swelling over the region of the thyroid, more marked on the right, and very tender. As far as could be determined, there had been no antecedent infection. The temperature was 99.6° F., pulse 120 and respirations 20. Examination disclosed a very sensitive right-sided thyroid adenoma, with a smaller, softer, less sensitive left lobe. The basal metabolic rate was -9.1. The symptoms subsided rapidly on simple management, although tenderness over the gland persisted for two weeks. One month later the metabolic rate was -1.1. The right lobe at this time was smaller, the nodule, however, being easily palpable.

**CASE III.**—Mrs. R. V., aged twenty-eight years, white, had a goiter for nine years. A normal pregnancy had terminated six weeks before admission, followed by a normal puerperium. Two weeks before coming under observation (four weeks after delivery) the goiter began to enlarge rapidly with marked pain and tenderness, headache, insomnia and nervousness. On admission her temperature was 101° F., pulse 120, and respirations 20. Examination revealed a considerably enlarged, symmetrical, moderately firm gland, exquisitely tender, hot, and over which the skin was reddened. Incision and drainage gave prompt relief, a considerable amount of pus being liberated.

**CASE IV.**—Mrs. E. B., aged thirty-four years, colored, stated that five days before admission she had had a sore throat. Three days later she noticed swelling and tenderness over the region of the thyroid with "sensation of choking." The temperature and pulse were normal when patient was first seen. The left lobe and isthmus of the thyroid were enlarged and sensitive. On palliative treatment the condition subsided.

CASE V.—Mr. E. K., aged twenty-three years, white, noticed rapid swelling of neck over the thyroid region five days before admission. For several days before this he had been coughing a good deal. The swelling was very sensitive, the neck "felt stiff," and there was some difficulty in swallowing. He had not been aware of a goiter. The temperature was 101° F., pulse 108, and respirations 20. The thyroid was symmetrically enlarged and very sensitive. A few diffuse moist râles were audible over the right lung. The condition declined satisfactorily on medical management.

CASE VI.—Mr. F. W., aged thirty-eight years, white, had a goiter for twelve years. Two weeks before admission, the right side of the gland began to enlarge rapidly and was accompanied by marked tenderness, chilliness, and night sweats. The patient thought the swelling was much "harder" than it had been. A loss of 25 pounds was said to have occurred within the few weeks before being seen. The temperature was 99° F., pulse 90, and respirations 24. Examination disclosed a symmetrically enlarged thyroid, the right lobe being the size of a small orange, irregular, and sensitive over its upper portion. A diagnosis of carcinoma of the thyroid was made, but at operation a large abscess of the right lobe was found.

CASE VII.—Mr. R. E., aged forty-seven years, colored, observed that three days before coming under observation, he had noticed a small but painful enlargement of "front of neck," with difficulty in swallowing, pain on moving head, and headache. The temperature was 100° F., pulse 78, and respirations 20. The pharynx was markedly injected, and the thyroid was diffusely enlarged and definitely sensitive. The condition subsided on palliative treatment.

CASE VIII.—Mr. J. W., aged twenty-five years, colored, was convalescing from a severe lobar pneumonia. Thirty days after the onset of the pneumonia the temperature rose to 101° F., and pain, tenderness and swelling were noted over the thyroid gland. Fluctuation soon became evident. Incision and drainage relieved the patient. Pneumococci were recovered from the pus.

The salient features of the above cases are summarized in the accompanying table.

TABLE I.—SUMMARIZING THE ESSENTIAL DATA IN THE EIGHT CASES REPORTED.

Case.	Age.	Sex.	Color.	Previous goiter.	Antecedent infection.	Type of thyroiditis.
I . . .	24	F.	W.	+	+	Simple.
II . . .	25	F.	W.	0	0	Simple.
III . . .	28	F.	W.	+	0	Suppurative.
IV . . .	34	F.	C.	0	(Pregnancy) +	Simple.
V . . .	23	M.	W.	0	+	Simple.
VI . . .	38	M.	W.	+	0	Suppurative.
VII . . .	47	M.	C.	0	+	Simple.
VIII . . .	25	M.	C.	0	+	Suppurative.

Summary.—1. Eight cases of acute thyroiditis are recorded, of which 3 were suppurative. They occurred mostly in the third decade, and were equally divided between sex and color. Antecedent infection had been present in 5, goiter in 3.

2. Acute thyroiditis, while occurring infrequently (about 0.1 per cent of all goiters) is sufficiently characteristic in its symptomatology to warrant prompt recognition.

3. The condition may be suppurative or nonsuppurative, and is usually secondary to some other infectious process, the site of the latter being most commonly in the respiratory tract.

4. The simple type of acute thyroiditis usually responds to proper medical treatment; the suppurative type demands prompt incision and drainage.

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## OPHTHALMOSCOPIC SIGNS IN DISEASE OF THE HEART.

### A STUDY OF ONE HUNDRED THIRTY-SEVEN CASES VERIFIED BY NECROPSY.\*

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OPHTHALMOSCOPY is becoming more and more important to the internist as an aid in diagnosis and prognosis. Relatively little has been written, however, on the subject of the examination of the ocular fundus in heart disease. In a review of the literature we found only two contributions which to us seemed significant. The first is in reference to subacute bacterial endocarditis. Horder, Herrick and others have called attention to the occurrence of petechiae and embolic lesions in the retina in some cases of this

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disease. The embolic lesions, when properly interpreted, are fairly pathognomonic. The other significant observation was first emphasized by O'Hare and Walker, namely, that evidence of preëxisting hypertension may be seen in the retinal arteries. Later, O'Hare, Calhoun and Altnow discussed the frequency of hypertension as a cause of "chronic myocarditis" and showed again the value of retinal signs of hypertension when the blood pressure at the time of examination is within normal limits. It seems that no one, however, has determined criteria in the fundus for differentiating the hypertensive and arteriosclerotic types of heart disease. In fact, clinicians often consider these two types of heart disease as occurring together and do not attempt to separate them. Nevertheless they are often distinct. In many cases in which the heart fails as the result of hypertension there is surprisingly little coronary sclerosis; and in cases in which marked coronary disease is found there may have been coëxisting hypertension and the heart may be hypertrophic, but it is the coronary sclerosis which has led to the cardiac breakdown. It was with the main idea in mind of differentiating ophthalmoscopically these two types of cardiac disease that we undertook this study. Also as far as we could ascertain, an extensive study with reference to changes in the fundi had not been made in patients with heart disease who were examined both during the course of the illness and at necropsy.

**Changes in Fundi Relevant to Cardiac Conditions.** Before recording the results of our study it will be necessary to describe briefly the various types of pictures in the fundus which we consider to be relevant to cardiac conditions, in order that we may refer to these types by name in our later discussion. In giving these descriptions we fully appreciate the lack of agreement among ophthalmologists in regard to the types of retinal arteriosclerosis and the forms of retinitis which may be associated with them. One of us (Wagener) previously has endeavored to classify the various forms of retinal arteriosclerosis.<sup>9</sup>

*Retinal Arteriosclerosis.* In this group of 137 cases, the retinal arteriosclerosis observed clinically was of two types, designated as the hypertension type and the senile type. Sclerosis of the retinal arteries (which are, of course, arterioles) of the hypertension type is characterized by generalized constriction of the caliber of the arteries with exaggeration of the arterial reflex stripe, irregularities in the lumen of the arteries, and arteriovenous compression (Fig. 1). The grading of the degree of sclerosis on a basis of 1 to 4 is estimated largely from the number and degree of the irregularities in the lumens of the arteries and partly from the severity of the generalized arterial constriction and the arteriovenous compression (Fig. 2). Retinal arteriosclerosis of the senile type is characterized by generalized reduction in the caliber of the retinal arteries without actual constriction and with dulling or loss instead of exaggeration of the

arterial reflex stripe (Fig. 3). There is slight, if any, irregularity in the lumen of the arteries and no arteriovenous compression. This type of sclerosis is usually mild, and is recognizable only after considerable experience.

*Retinitis.* Varieties of retinitis met with in this series of cases are found only in association with retinal arteriosclerosis of the hypertension type. The retinitis of severe benign hypertension is characterized by scattered cotton-wool patches and hemorrhages, and mild, more or less generalized, edema of the retina, in which in the later stages powdery, punctate, white exudates may appear (Fig. 4). In the retinitis of malignant hypertension, to this picture is added edema of the disk which may vary in degree from mere hyperemia and marginal blurring to an elevation of several diopters (Fig. 5). The edema of the retina is usually, but not necessarily, more extensive than in the retinitis of benign hypertension, and punctate exudates of residual edema are, therefore, more commonly seen and may be of sufficient number in the macular region to form a more or less complete macular star. The retinitis of malignant hypertension has been more fully considered in a paper by Keith, Wagener and Kernohan.

*Retinal Petechiæ and Embolic Lesions.* The retinal petechiæ sometimes seen in subacute bacterial endocarditis, like those in the conjunctiva, are rounded and have a small, yellowish-white nucleus or center. As noted by Moore, other types of hemorrhages may be found; they may be flame-shaped, perivascular and subhyaloid in type. Some of the hemorrhages are no doubt dependent on the associated secondary anemia. In one of our patients retinitis was present which could not be distinguished from that seen in pernicious anemia. Another patient, who is not included in this series, showed retinitis with papilledema similar to that described by Falconer and probably allied in nature and origin to the septic retinitis of Roth. We interpret as embolic ischemic lesions certain isolated, grayish-white patches in the retina and choroid. We have seen these alone and also associated with typical petechiæ. One of our patients had scattered areas of choroidal atrophy and pigmentation which may have been the late result of emboli in the choroidal arteries. Another who did not come to necropsy had a non-septic embolus of the central artery of the retina.

**Cardiac Conditions Concerned.** This report is based on the study of the ocular fundi in 137 cases of cardiac disease. These cases were classified as follows:

Chronic endocarditis (rheumatic)	31
Subacute bacterial endocarditis	8
Syphilitic aortitis and endocarditis	6
Adenomatous goiter with thyrotoxicosis	10
Exophthalmic goiter	6
Hypertension	32
Coronary sclerosis	25
Mixed types	11
Indeterminate	8

Necropsy was performed in all of the cases, so that the diagnosis of the type of heart disease was as accurate as is possible in a combined study of the clinical course and the pathologic anatomy in each case. The dominant etiologic factor was used as the basis of classifying the cases. Certain qualifications must be noted regarding this classification. In the 32 cases listed as hypertension\* there was no other known factor which might cause the cardiac failure. The degree of coronary sclerosis in all of these cases was graded less than 3. In placing cases in the group of coronary sclerosis, the degree of sclerosis of the coronary arteries was the deciding factor; they all showed sclerosis of these vessels graded 3 or 4. A large number of these patients, however, had had hypertension, but the marked degree of coronary sclerosis was considered the important feature in the cardiac failure. In the group of chronic endocarditis some of the patients had hypertension, but the endocarditis apparently was the more important factor. The same was true in the groups made up of patients with goiter. The group of mixed types included those cases which showed two or more factors relevant to the cardiac failure, no one of which could be determined as the dominant factor.

*Chronic Endocarditis (Rheumatic).* Of the 31 cases in this group there were sixteen men and fifteen women. The youngest patient was aged twenty-one years, the oldest, seventy-seven, and the average age was fifty-four. There were 16 cases of mitral endocarditis, 7 cases of combined mitral and aortic endocarditis, 4 cases of aortic endocarditis, 1 case of combined mitral, aortic and tricuspid endocarditis, and 1 case of tricuspid endocarditis. In 17 cases, cardiac failure alone was the cause of death and in 14 cases cardiac weakness was definitely contributory. The fundi were normal in 19 and showed changes in 12; 2 of the 12 had inactive inflammatory lesions. One showed merely spontaneous arterial pulsation, due to aortic regurgitation. Another had retinitis of glomerulonephritis and a fifth had choroidal arteriosclerosis. Seven cases had retinal arteriosclerosis, of which 3 were of the hypertension type and 4 of the senile type.

*Subacute Bacterial Endocarditis.* Of the 8 cases 3 were males and 5 were females. The youngest patient was aged eleven years, the oldest, fifty-eight, and the average age was thirty-one and five-tenths years. Death was due to septicemia in all cases. Three had renal lesions, one had cerebral infarcts and meningitis and one had bronchopneumonia. The fundi were normal in 4 cases. One of the 4 cases with lesions in the fundus showed choroidal scars possibly of embolic origin. Another had retinitis of anemia. Two had embolic ischemic lesions. This type of lesion is of great diagnostic importance if properly interpreted. Petechiae were not observed

\* Blood pressure of 160 systolic and 90 diastolic was arbitrarily chosen as the upper limit of normal.

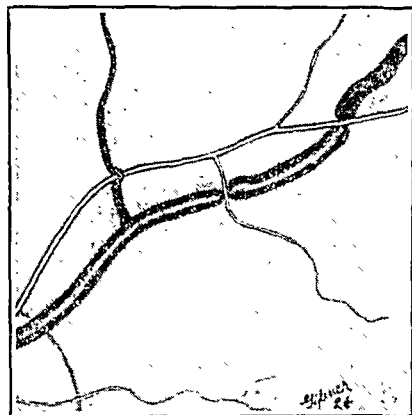


FIG. 1.—Retinal arteriosclerosis of the hypertension type, graded 1.

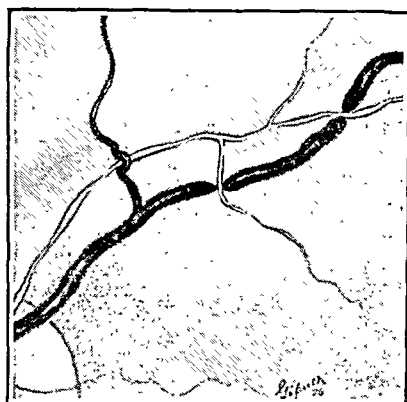


FIG. 2.—Retinal arteriosclerosis of the hypertension type, graded 3.

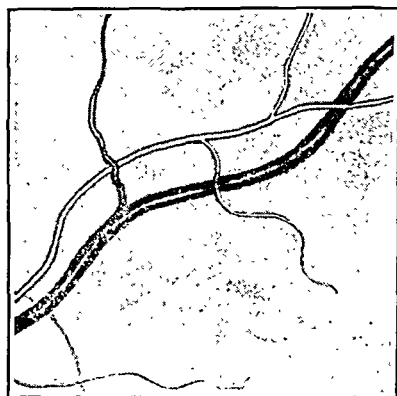


FIG. 3.—Retinal arteriosclerosis of the senile type.

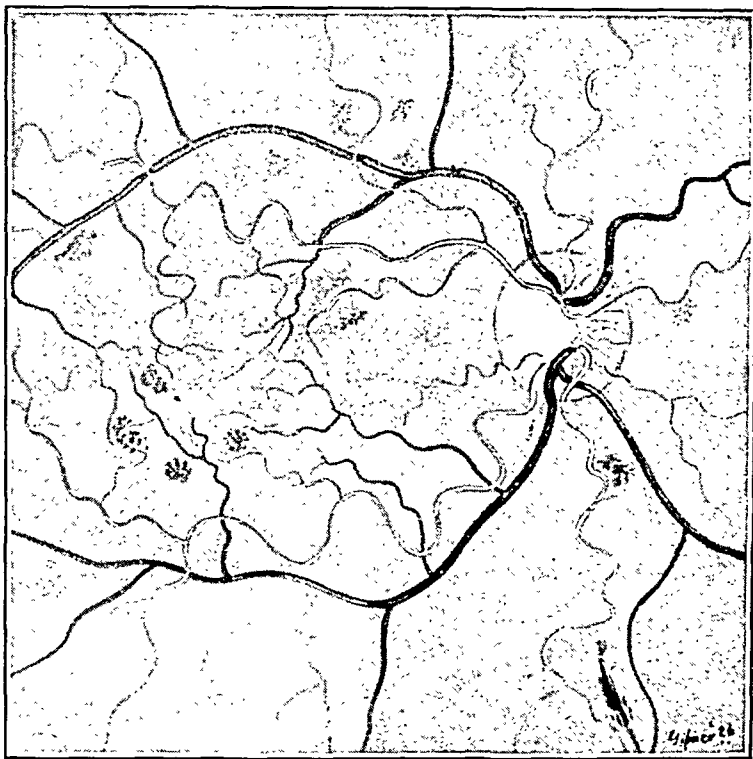


FIG. 4.—Retinitis of severe benign hypertension.

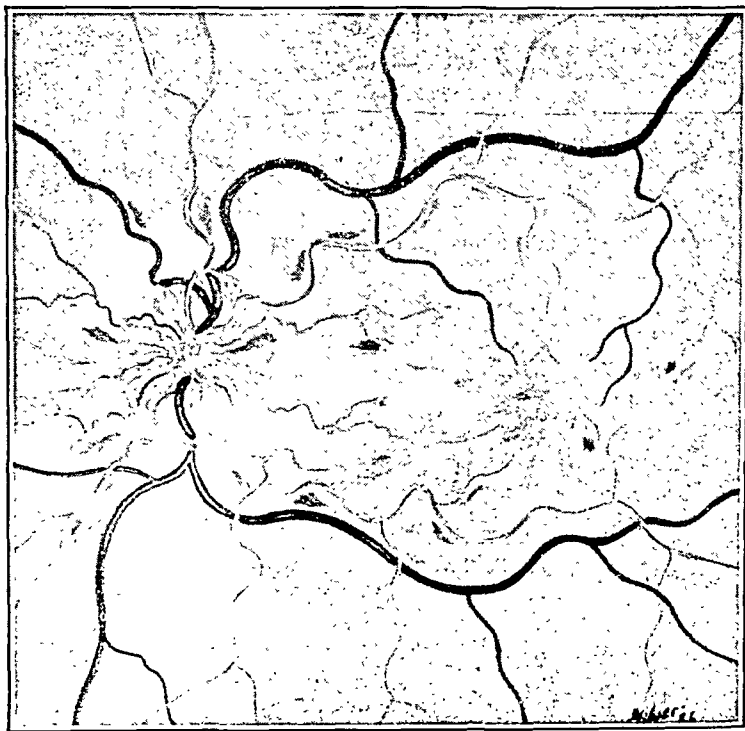


FIG. 5.—Retinitis of malignant hypertension.

in any of these cases but we have noted them in other cases. When present in cases of septicemia, they are of considerable diagnostic importance.

*Syphilitic Aortitis and Endocarditis.* Of the 6 cases 4 were men and 2 were women. The youngest patient was aged thirty-one years, the oldest, fifty-two, and the average age was thirty-nine. The clinical course of all of these cases was that of pure cardiac failure. Only one had changes in the fundi and they were merely those of old choroiditis. Cases of aortic regurgitation often show arterial pulsation in the retina, but this is not of real diagnostic value, since the other signs of regurgitation usually are quite prominent. The pulsation probably denotes only a high pulse pressure.

*Adenomatous Goiter with Thyrotoxicosis.* These 10 patients all had definite symptoms of cardiac injury. One died of cardiac decompensation and 9 died after operation on the thyroid gland, apparently from cardiac failure. There were 2 men and 8 women. The youngest patient was aged thirty-five years, the oldest, sixty-eight, and the average age was fifty-seven. The fundi showed changes in one case; in this case there was mild senile fibrosis of the retinal arteries.

*Exophthalmic Goiter.* Six cases had evidence of cardiac injury. All were women. The youngest patient was aged forty-three years, the oldest, sixty, and the average age was fifty-one. Two died of pure cardiac failure. Four died after operation on the thyroid gland. The fundi were normal in 3 cases. In 1 case there was slight choroidal degeneration with mild sclerosis of the choroidal vessels. Another case showed postinflammatory choroidal lesions. One case showed a mild degree of sclerosis of the retinal arteries of hypertension type.

*Hypertension.* This group consisted of 32 cases of both benign and malignant types, of which 14 were males and 18 females. The youngest patient was aged thirty years, the oldest, sixty-nine and the average age was fifty-six. Twenty-five patients died of cardiac decompensation or cardiac decompensation associated with uremia, 4 of hemiplegia, 2 after operations, and 1 patient died after an accident. In 31 cases the fundi showed sclerosis of the retinal arteries of hypertension type. In addition to this change, 17 showed retinitis, 11 being of the malignant type and 6 of the benign type. In 3 other cases there were a few areas of hemorrhage in the retina. The degree of severity of the retinal changes was listed as follows: 9 graded 1, 13 graded 2, and 9 graded 3.

*Coronary Sclerosis.* Twenty-five cases were classified in this group. Twenty were men and 5 women. The youngest patient was aged forty-five years, the oldest, eighty-two, and the average age was sixty-one and five-tenths years. Nineteen deaths were due to causes purely cardiac, either congestive or anginal, and 6 patients died after operations. The fundi were negative in 2 cases.

In one other case sclerosis of the choroidal vessels only was present. There were 7 cases in which the fundus changes were classified as senile sclerosis of the retinal arteries, 10 classified as retinal arteriosclerosis of hypertension type and 5 not classified. These unclassified cases were, however, of one or the other of these two types of retinal arteriosclerosis. The degree of change in the senile type was graded 1 in all. In the cases with signs of hypertension 3 were graded 1, 5, graded 2, and 2, graded 3; none had retinitis, but 2 had some areas of hemorrhage. Of those not classified as to type of sclerosis, there were 2 graded 4 and 3 graded 2.

*Mixed Types.* There were 11 cases in which two or more factors were present which were of importance in the cardiac failure, no one of which could be considered of greater importance than the others. Two were men and 9 women. The youngest patient was aged thirty-seven years, the oldest seventy-three, and the average age was fifty-nine. Six patients died of cardiac failure, 2 died of uremia, 2 died after apoplexy and 1 patient died with pneumonia. In 3 cases, hyperthyroidism due to toxic adenoma and hypertension were present; in 2 exophthalmic goiter and hypertension coëxisted; in 2 there was hyperthyroidism due to toxic adenoma, hypertension and coronary sclerosis; in 1 case the combination of toxic adenomatous goiter with hypertension and endocarditis was noted; in one hypertension and endocarditis, in one hypertension, coronary sclerosis and endocarditis, and in one malignant hypertension and syphilitic aortitis and endocarditis. The fundi were normal in 2 cases. In the other 9 there was sclerosis of the retinal arteries, either of hypertension or senile type, with benign retinitis in 1 case and malignant retinitis in 1.

*Indeterminate Types.* Of the 8 cases in which a causal factor was not established there were 5 men and 3 women. The youngest patient was aged forty-two years, the oldest, seventy, and the average age was fifty-seven. All died of cardiac failure alone except one who had pernicious anemia. The fundi did not show changes in 6 cases. In 1 of the other 2 (the case with pernicious anemia) there was retinitis of severe anemia, and in the other there was mild sclerosis of the retinal arteries of hypertension type. In the latter case the blood pressure was only 142 systolic and 76 diastolic, but the heart weighed 635 gm. (normal weight estimated at 250 gm.).

**Changes in Fundi Significant of Particular Cardiac States.** The only types of changes in the fundi which were of significance in the estimation of the cardiac status in these 137 cases of heart disease were, then, the embolic lesions in subacute bacterial endocarditis, and the sclerosis of the retinal arteries either of the hypertension or senile type and with or without retinitis. The embolic lesions of subacute bacterial endocarditis constituted the only specific changes in the various types of heart disease as far as diagnosis was concerned. This point having been established, we desired to know what was

the significance of the two types of retinal arteriosclerosis, the hypertension and the senile type, and what the association of retinitis with the hypertension type denoted.

Of the 137 cases of heart disease, 72 showed sclerosis of the retinal vessels of one or the other of the two types. There were 52 classified as the hypertension type, 13 as the senile type, and 7 unclassified as to type. Nineteen of the cases with sclerosis of the hypertension type showed retinitis. The distribution of the retinal arteriosclerosis and the retinitis of hypertension in the different groups of cardiac disease is shown in the tabulation.

*Retinal Arteriosclerosis in Heart Disease in General.* Of the 52 cases in which there was retinal arteriosclerosis of hypertension type 50 were cases of hypertension. In the other 2, the hearts were large and hypertension had probably been present at some time. On the other hand, there were 6 cases of the 137 in which there was hypertension but in which the fundi appeared normal. Of the 13 cases in which there was retinal arteriosclerosis of the senile type, 12 were cases of hypertension, and the other case was a case of coronary sclerosis in which the heart weighed 540 gm., so that it may be assumed that hypertension had been present at one time. In the 7 cases in which the type of sclerosis was not classified, hypertension was present in all. Therefore, in all but 3 of the cases in which retinal arteriosclerosis of either hypertension or senile type was found, hypertension was present, and in these 3 there was reason to believe that hypertension had at one time existed. This suggested that either type of retinal arteriosclerosis is equally indicative of the presence of hypertension.

INCIDENCE OF RETINAL ARTERIOSCLEROSIS AND OF THE RETINITIS OF HYPERTENSION IN THE DIFFERENT GROUPS OF HEART DISEASE IN WHICH THEY OCCURRED.

Classification of cardiac disease.	Cases.	Retinal arteriosclerosis of hypertension type.	Retinitis of hypertension.	Retinal arteriosclerosis of senile type.	Retinal arteriosclerosis unclassified as to type.
Chronic endocarditis . . . . .	31	3		4	
Adenomatous goiter . . . . .	10			1	
Exophthalmic goiter . . . . .	6	1			
Hypertension . . . . .	32	31	17		
Coronary sclerosis . . . . .	25	10		7	5
Mixed types . . . . .	11	6	2	1	2
Indeterminate . . . . .	8	1			
Total . . . . .	123	52	19	13	7

The question naturally arose as to the significance of the senile and hypertension types of retinal arteriosclerosis. Attention first was directed to the senile type. Four patients were in the endocar-



ditis group and one in the group of toxic adenomatous goiter. Considering the 4 cases in the endocarditis group in which this type of retinal arteriosclerosis existed all the patients were aged more than sixty-nine years and the hypertension was not severe in any cases at the time of examination. The 1 patient in the group with toxic adenomatous goiter was aged sixty-eight years and the hypertension was mild at the time of examination. The hearts of 4 of these 5 cases were only mildly or moderately hypertrophied; marked hypertrophy was present in only one case, which was a case of aortic stenosis. Scleroses of the coronary arteries were not graded more than 2 in any case. In the 7 cases with this type of fundus picture in the group of coronary sclerosis the average age was sixty-five years and the degree of hypertension was not great at the time of examination. The coronaries were sclerosed, graded 3 to 4 in all. Only two of the hearts weighed more than 600 gm. In the one case in the group of mixed types the patient was aged seventy-three years, the hypertension was of only moderate severity and the coronary vessels were sclerotic, graded 3; the heart weighed 505 gm. In all cases, therefore, showing the senile type of retinal arteriosclerosis the average age was sixty-nine years and the hypertension apparently was mild. The degree of retinal arteriosclerosis was graded 1 in all but 3 cases, which were graded 2.

Turning next to a consideration of the 52 cases of all groups showing the hypertension type of retinal arteriosclerosis we found the average age to be fifty-six years; the hypertension was, on the whole, more severe, and the hearts were, as a rule, much more hypertrophied. Only 3 did not have hypertension at the time of examination. In 19 the sclerosis was graded 1, in 21, graded 2, and in 12 graded 3. There were 7 with the retinitis of benign hypertension, 12 with the retinitis of malignant hypertension and 7 with a few areas of retinal hemorrhage. All of those with retinitis had severe cardiac disease, apparently due mainly to the hypertension, and all of those with the malignant type had evidence of renal injury in addition to cardiac injury.

*Retinal Arteriosclerosis in Heart Disease Due to Hypertension and Coronary Sclerosis.* Surveying next only the two groups of cardiac disease due to hypertension and coronary sclerosis it was noted that the average age of those in each group with retinal arteriosclerosis of hypertension type was fifty-six years and the average age of those with retinal arteriosclerosis of senile type was sixty-five. The senile type occurred, however, only in the group of coronary sclerosis. The cases in the group of coronary sclerosis with the senile type of change showed evidence of a milder type of hypertension, either in the degree of hypertension or in the degree of hypertrophy of the heart.

Attention must be called to the 6 cases of the 137 in which hypertension was present without the presence of retinal arteriosclerosis

of either the hypertension or the senile type. Two of these were cases of exophthalmic goiter, 2 were cases of chronic endocarditis, 1 was a case of toxic adenomatous goiter with chronic endocarditis and hypertension, and one was a case of toxic adenomatous goiter with hypertension. In the first 2 cases the hypertension was mild and the hearts were only moderately hypertrophied, but in the other 4 cases the hypertension was fairly severe in all, although the hearts were not greatly hypertrophied. In 1 of the latter, the hypertension was of ten years' known duration.

**Summary.** A series of 137 patients with heart disease who had had their ocular fundi examined and who came to necropsy was studied to determine the value of ophthalmoscopy in the diagnosis and prognosis of heart disease. The series included a fairly representative group of each of the main types of heart disease.

Only three types of changes in the fundi relevant to the cardiac disease were observed, and only one of these was pathognomonic; namely, the embolic lesions in subacute bacterial endocarditis. These lesions, however, are difficult of interpretation by those unfamiliar with the picture. The other two types of changes, although not pathognomonic of heart disease, are of value in diagnosis and prognosis. These are the two main types of retinal arteriosclerosis, the hypertension type, with or without associated retinitis and the senile type, both of which are found in association with hypertension.

When retinal arteriosclerosis of hypertension type is found, it always signifies that hypertension is present or has been present, a fact which has been amply shown by other authors. On the other hand, the absence of this fundus picture does not exclude hypertension, since the retinal changes are not found in a small percentage of cases. If they are present in a patient with heart disease, less than sixty years of age, who does not have other evident cause for such disease, hypertension may be assumed to be the cause. If in addition to the retinal arteriosclerosis retinitis of the hypertension type is present, hypertension is always the most important factor in the cardiac disease; and the course of this disease is likely to be more rapid and severe than in cases in which retinal arteriosclerosis alone is present. If, however, retinal arteriosclerosis of hypertension type without retinitis is present in patients old enough to be the subject of severe coronary sclerosis, the existence of this type of fundus picture indicates only that hypertension is or has been present. One must rely in such cases on the symptoms for the interpretation of the degree of sclerosis of the coronary arteries.

Retinal arteriosclerosis of senile type occurs in older persons aged more than sixty, usually with hypertension. The hypertension in such cases usually is not severe, and if cardiac disease exists, the hypertension may be excluded as the important causal factor

and severe coronary sclerosis may be assumed to be present. Stated otherwise, if an older person with cardiac disease and hypertension but without evidence of toxic goiter or endocarditis, has retinal arteriosclerosis of the senile type he probably has severe coronary sclerosis. On the other hand, in such a person the presence of the hypertension type of retinal arteriosclerosis does not allow one to exclude the existence of serious coronary sclerosis. We may assume, then, that persons who live long enough with hypertension for a pathologic degree of coronary sclerosis to develop, or whose cardiovascular system has accommodated sufficiently to the hypertension to allow of a longer span of life, have had a milder degree of arteriolar disease and probably have been originally endowed with a more potentially flexible coronary circulation. It is probable that what we designate as retinal arteriosclerosis of the senile type is the resultant of a longer standing but milder hypertension. On the whole, we have found that the patients in the group of coronary sclerosis have milder hypertensive disease than those in the hypertension group, irrespective of whether the retinal arteriosclerosis is of the hypertension or of the senile type.

**Conclusions.** 1. In this study about 90 per cent of patients with heart disease who have hypertension show some degree of retinal arteriosclerosis.

2. About 96 per cent of patients with heart disease due to hypertension alone show retinal arteriosclerosis of the hypertension type.

3. About 92 per cent of patients with heart disease due mainly to coronary sclerosis have retinal arteriosclerosis of either the hypertension or the senile type.

4. In any case of heart disease in which there is retinal arteriosclerosis of either the hypertension or the senile type, therefore, hypertension or coronary sclerosis may be of importance in reference to the cardiac failure. Conversely, in any case of heart disease in which retinal arteriosclerosis is not present the heart disease is usually not due to either hypertension or coronary sclerosis.

5. If a patient with cardiac disease and hypertension, and without evidence of toxic goiter or endocarditis, has retinal arteriosclerosis of the senile type, he probably has coronary sclerosis of severe degree.

6. The presence of retinitis, of benign or malignant hypertension type, in heart disease indicates severe arteriolar disease due to hypertension and warrants a more serious prognosis than the same grade of retinal arteriosclerosis alone.

7. Ophthalmoscopic examination yields negative results in cases of heart disease unless the heart disease is due to or associated with hypertension or coronary sclerosis, or subacute bacterial endocarditis.

8. In subacute bacterial endocarditis, the presence of embolic lesions or petechiæ in the retina is practically pathognomonic.

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## BRUCELLA ABORTUS IN MILK SUPPLY AS A SOURCE OF AGGLUTININS IN HUMAN SERA.

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THE report of Evans, in 1918, of the close relationship between *Brucella melitensis* and *Brucella abortus* renewed interest in the possibility of human infection with the Bang bacillus. *Brucella abortus* was first isolated from a human source in 1924 by Keefer. In the following years cases of *Brucella abortus* infection of bovine origin have been reported from various parts of this country as well as from Europe and Africa. In 1926, Moore and Carpenter reported 12 cases from New York; Huddleson, 6 from Michigan; and Dickson, one case from California. In 1927, Belyea reported one case from Washington; Hull and Black, 4 cases from Illinois; Gilbert and Coleman, 15 cases from New York; and Evans summarizes 20 cases from different parts of the United States but includes porcine as well as bovine infection. Among the cases reported in 1928 are 83 by Hardy from Iowa; 7 by Sensenich and Giordano from Indiana; and one by Scott and Saphir from Ohio; McAlpine and Mickle, and others, report evidence of infection in Connecticut; and Kern reports one case from Pennsylvania and one from Virginia and summarizes some of the cases previously reported.

The diagnosis in July, 1926, of a case of undulant fever at the Metropolitan Life Insurance Company Sanatorium at Mount McGregor led to a study of the herd supplying the sanatorium with milk, and later to a study of the sanatorium patients. Agglutination tests for *Brucella abortus* were made on the blood serum from each patient admitted; the sera of the cows were tested for agglutinins at intervals of from two to five months and their milk was inoculated into guinea pigs for the detection of *Brucella abortus*.

The sanatorium, maintained for disabled employees of the company forms an isolated community on Mount McGregor. Grade A raw milk is supplied from one of the company farms in the valley nearby. The dairy is well equipped and handled and the milk counts seldom exceed 500 bacterial colonies per cubic centimeter. According to accepted bacteriologic standards, the patients receive raw milk of exceptionally high quality.

**Studies on the Herd.** Agglutination tests were done every two months for the first six months and then at intervals of from three to five months, making a total of nine tests. For the testing, serum dilutions of 1 to 60, 1 to 120, 1 to 180 and 1 to 540 are used and agglutination at 1 to 120 is considered evidence that the animal is infected, while agglutination at 1 to 60 is suggestive of infection. Of the sera of 151 cows bled in December, 1926, 56 agglutinated at 1 to 120 or higher, and 26 at 1 to 60, while 69 did not agglutinate *Brucella abortus* No. 80. In September, 1928, 118 cows were bled; 37 showed agglutinins in serum dilutions of 1 to 120 or higher, 10 in 1 to 60, while 71 were negative.

Cultural studies were made on the blood of all the cows in the herd and on the urine of five infected cows. We were unable to isolate *Brucella abortus* from any of this material.

**Studies on the Milk.** A sample of the milk from each cow is inoculated intraperitoneally into at least one guinea pig. Six weeks later the guinea pigs are killed and carefully autopsied. The spleen is removed aseptically and cultured on serum agar in an atmosphere of 10 per cent CO<sub>2</sub>. Abortus infection is evidenced by the enlargement of the spleen with the formation of tubercle-like lesions, the presence of small necrotic foci—1 to 2 mm. in diameter—in the liver, abscess formation in the epididymis, and sometimes by joint involvement. The blood sera of infected guinea pigs agglutinate *Brucella abortus* No. 80 in dilutions of 1 to 135 or higher and the spleen cultures are invariably positive.

The milk from each cow in the herd is thus studied at frequent intervals. From milk samples of 24 cows we have obtained cultures of *Brucella abortus*. Twenty-three of these animals had serum titres of 1 to 120 or higher. The twenty-fourth cow possessed no agglutinins in her serum at the time of the first, and of the second positive milk culture. Later her serum gave partial agglutination at 1 to 120. This is the only cow in this herd whose milk showed evidence of infection before agglutinins appeared in her blood serum.

Although we have never been able to obtain *Brucella abortus* from the milk of cows whose serum titre is 1 to 60, neither have we been able to recover this organism from the milk of 33 of the 56 cows with titres of 1 to 120 or more. Eleven of these animals whose milk was not infected, had agglutinin titres ranging from 1 to 1000 to 1 to 32,000. Therefore, a high serum titre does not necessarily indicate that a cow is discharging *Brucella abortus* in her milk.

We have always obtained positive cultures from the milk of a few of the cows. With many of the infected cows, however, at least one milk sample has failed to infect guinea pigs. This suggests that the organisms may be present in very small numbers or that they are not being continuously discharged into the milk.

**Studies on the Patients.** Dilutions of 1 to 15, 1 to 45 and 1 to 135 are used routinely on human sera and an agglutination at 1 to 15 is considered significant.

During a period of a little less than two years, we have studied the blood sera of 851 patients and 155 staff members for agglutinins. Ninety-one or 9 per cent of these agglutinated *Brucella abortus* No. 80 in dilutions of 1 to 15 or higher. Twenty-four of the 91 had titres varying from 1 to 45 to 1 to 3200. In some instances the agglutinins persisted in the blood from six to eighteen months.

The patients, all adults, come from cities in all parts of the United States and Canada, although the majority are from the Home Office of the Company in New York City. Forty-four, or 48 per cent, of the patients had diagnoses of tuberculosis; 10, chronic tonsillitis or sinusitis; and 6, ulcerative conditions of the intestinal tract; while the remainder suffered from various diseases.

Milk forms an important part of the sanatorium diet, and the patients, because of pre-existing illness, were doubtless very susceptible to the abortus infection of the milk supply. The staff members for the most part had no clinical symptoms at the time of their positive agglutination but it is of interest that this portion of the staff find sanatorium life expedient or desirable if they are to work at all.

In a few cases, symptoms of undulant fever were very apparent. The patients were confined to bed, gave agglutination titres of 1 to 1200 or higher and had a leukopenia with a relative lymphocytosis.

One case is of particular interest clinically. The patient had severe pains in the lumbar region and his temperature ranged from 98.6° to 103.6° F. Since he had a history of tuberculosis, Pott's disease was for a time suspected. Later his symptoms were found to be due to *Brucella abortus* infection which was apparently localized in the paravertebral lymph nodes. The leukocyte count was 5200 with 57 per cent polymorphonuclears, 29 per cent lymphocytes and 13 per cent mononuclears. The first blood sample, taken shortly after the onset of symptoms, agglutinated *Brucella abortus* No. 80 at 1 to 45. Other samples were taken at three- to five-day intervals. A higher serum titre was obtained with each successive specimen

but the blood cultures were negative. Blood collected twelve days after the first sample had a serum titre of 1 to 1440 and from it *Brucella abortus* was isolated by culture and by guinea-pig inoculation. Agglutinin absorption tests demonstrated the organism to be the abortus variety of *Brucella melitensis*. This culture produced abortion when inoculated by Carpenter into the mammary duct of a pregnant heifer.

One patient from Maine was referred to the sanatorium because of suspected incipient tuberculosis; this diagnosis was not confirmed but he was found to be suffering from undulant fever. He had then been ill for several months and had a serum titre of 1 to 3200. We were unable to isolate *Brucella abortus* from his blood. The leukocyte count of this patient, Mr. L., and of two other typical cases of undulant fever are tabulated below.

Patients.	Serum titre.	Total leukocytes.	Per cent polymorpho-nuclears.	Per cent lymphocytes.	Per cent mono-nuclears.
Mr. L. . . .	3200	7800	35	54	9
Miss C. . . .	480	5700	25	68	7
Mr. J. . . .	1280	5800	42.5	47	9.5

The majority of the patients had very mild symptoms which were usually referred to manifestations of other diseases. Undulant fever as an entity was seldom recognized by the clinician and the evidence of the agglutination test was frequently the outstanding indication of abortus infection. The majority of the staff, even those with titres of 1 to 45 or higher, went about their work either asymptomatic or attributing their symptoms to some more obvious cause. In fact, several of the bloods from staff members were taken primarily because of interest in other serological tests and infection with *Brucella abortus* was entirely unsuspected.

Blood samples were routinely taken from the patients during their first week of residence. Agglutinins were frequently present in the serum at this time, although in some instances they were produced rather slowly, the initial negative finding being followed after some months by a positive one. One staff member was negative when first tested but nine months later his serum agglutinated at 1 to 45 and this titre has persisted for over a year.

From November 29, 1926, to November 17, 1927, the sera of 510 patients and 89 staff members were tested and 82 of these contained agglutinins. Seventy-one of the 82 sera were from patients and 11 were from staff members. By the end of this period, the cows producing infected milk had been segregated.

From November 18, 1927, to June 16, 1928, no sera which agglutinated even in a dilution of 1 to 15 were obtained from the 228 new patients admitted nor from the 42 additional staff members tested, although many of the earlier cases maintained fair titres. During this period of seven months, the guinea-pig inoculations indicated that the milk was free from abortus organisms.

From June 27, 1928, to November 1, 1928, sera from 113 new patients and 24 staff members were examined and agglutinins were present in 9 of these. These findings indicated that the milk was again infected. There was in the herd one young cow with an agglutinin titre of 1 to 2000. Her milk had failed to infect guinea pigs at the beginning and at the middle of this, her first, lactation period. A guinea pig inoculated with a third sample showed that she was discharging *Brucella abortus* in her milk. According to our records, the other cows whose milk was used raw, were all producing abortus-free milk and this one animal was doubtless responsible for the production of agglutinins in the sera of some of the new patients.

**Discussion.** We have submitted data indicating that the ingestion of raw milk infected with *Brucella abortus* produces agglutinins and causes undulant fever in man. When this study was begun in 1926, we were aware of the presence of infectious abortion in our dairy herd but we had no evidence that the milk might be a menace to the health of the sanatorium patients and staff. In fact, when we instituted routine agglutination tests for *Brucella abortus*, we expected that some of our patients, like Mr. L., might be coming to us already ill with undiagnosed undulant fever. Hence agglutination tests were done routinely within a week of admittance to the sanatorium and comparatively few of the patients were tested after longer residence. It is surprising, perhaps, that agglutinins were produced so promptly after drinking infected milk, but this has been verified by the unpublished results of our feeding experiments with monkeys. Eyre reports that agglutinins frequently appear in the blood of Malta fever patients by the fifth day and sometimes earlier.

The patients were all from cities or towns and, as a rule, had not drunk raw milk until they came to the sanatorium where it became an important part of their diet. In the majority of instances, the symptoms were mild or attributed to manifestations of other diseases and undulant fever would not have been recognized if routine agglutination tests had not been made. This study indicates that the presence of agglutinins in human sera, even in low dilutions, is due to infection with *Brucella abortus*. When the sanatorium patients were all consuming raw infected milk, only a portion of them developed agglutinins for *Brucella abortus* and when there was no *Brucella abortus* infection of the milk, agglutinins were not produced in the sera of the patients.

Goats have never been kept on any of the company farms nor are they kept on any of the adjacent farms.

Swine are kept on one of the group of Metropolitan Life Insurance Company farms but not upon the dairy farm and the swineherds have no contact with the dairy or with the cattle. All milk fed to the pigs is pasteurized. There is no history of contagious abortion in the swine.

The evidence in this study, and especially the correlation between



the periods of *Brucella abortus* infection of the milk supply and the appearance of agglutinins in the sera of the patients, indicate a bovine rather than a porcine origin of our cases. Carpenter and King in their summary of 155 reported cases of undulant fever find that only 7 had any possible contact with swine. Hardy in his report of 83 cases in Iowa states that 11 of the infections were acquired from swine.

The similarity between Malta fever and infection with *Brucella abortus* has been discussed at length by Evans and others. *Brucella melitensis* and *Brucella abortus* are morphologically and biologically similar but may be differentiated by means of the agglutinin absorption test. Clinically, the two diseases are quite similar but *Brucella abortus* infection is usually less severe than infection with *Brucella melitensis* although there are many mild ambulatory cases of the latter on record, some without subjective symptoms. It is said that Malta fever is seldom recognized in its early stages, even in countries where it is known to be endemic, and the same appears to be true regarding *Brucella abortus* infection in the United States. Shaw isolated *Brucella melitensis* from 10 of 22 apparently healthy dock hands in Malta. Carpenter reports *Brucella abortus* from the blood of a patient with an agglutinin titre as low as 1 to 5 and has obtained the organism from 4 patients who had no demonstrable agglutinins in their sera. Keefer continued to isolate *Brucella abortus* from his patient for several weeks after the fever and symptoms had subsided. Is it then surprising that undulant fever from bovine sources has been overlooked for years and that many cases are undiagnosed in parts of the country where raw milk is consumed? As Evans says: "The majority of cases of abortus infection which have been recognized in this country were found by a few observers, who, having had their attention directed to the disease by the recognition of one case, were able to find other cases by looking for them."

**Summary.** 1. Individuals with lowered resistance, who drink raw milk infected with *Brucella abortus* may develop agglutinins in their blood serum with or without the manifestation of appreciable clinical symptoms of undulant fever. Of 851 patients and 156 staff members in a sanatorium using raw milk, 91 or 9 per cent showed abortus agglutinins when their sera were diluted 1 to 15 or higher. Twenty-four of the 91 had agglutinin titres varying from 1 to 45 to 1 to 3200.

2. The presence of abortus agglutinins in human serum is evidence of infection with *Brucella abortus*. The agglutinins may persist in the serum for months or years after the recovery of the patient.

3. There is complete lack of evidence of porcine infection in our herd. The correlation between the periods of *Brucella abortus* infection of the milk supply and the occurrence of agglutinins in

the sera of the patients indicates a bovine origin of the cases of undulant fever reported in this study.

4. *Brucella abortus* may be present in small numbers in the milk of infected cows but the organisms may be eliminated for several years.

5. The presence of *Brucella abortus* agglutinins in the blood sera of cows does not determine whether they are discharging *Brucella abortus* in their milk. In a herd of 151 animals, no evidence was obtained of the infection of the milk of cows whose sera agglutinate at 1 to 60, while cultures of *Brucella abortus* were obtained from the milk of only 23 cows out of 56 with titres of 1 to 120 or higher.

6. *Brucella abortus* was not isolated from the blood or from the urine of the infected cows.

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## REVIEWS.

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THE SURGICAL OPERATIONS ON PRESIDENT CLEVELAND IN 1893  
TOGETHER WITH SIX ADDITIONAL PAPERS OF REMINISCENCES.  
By WILLIAM W. KEEN, M.D., Emeritus Professor of Surgery,  
Jefferson Medical College, Philadelphia. Pp. 251. Philadelphia  
and London: J. B. Lippincott Company, 1928.

REMINISCENCES of prominent medical men are apt to be interesting, especially if well written, as this is; but as this collection has the additional advantage of presenting first-hand evidence of almost seventy years of professional experience, one can only wish that the modest volume were triple its length. The author, who is now in his ninety-third year (how many authors are there in the nineties?), assisted at an operation on a soldier of Napoleon; after heard his grandmother tell of her meetings with Washington at Valley Forge; was an active surgeon throughout the Civil War and has witnessed more great medical discoveries than had been made in the previous eighteen centuries of the Christian era! In the article on Pasteur a keen comparison of that scientist's pre-paralytic and postparalytic achievements is to be found; the evaluation of Weir Mitchell evinces the advantages of an intimate but unbiased friendship; while "Sixty Years of Surgery" speaks for itself. "What it Costs to Become a Doctor," "An Episode of the Second Battle of Bull Run," and "The Eighty-fourth Birthday" complete the list.

E. K.

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THE KAHN TEST. A PRACTICAL GUIDE. By R. L. KAHN, M.S.,  
Sc.D., Director of Laboratories of the University Hospital, and  
Resident Professor of Clinical Bacteriology and Serology to the  
University of Michigan. Pp. 201; including 6 plates, 6 charts  
and 12 tables. Baltimore: Williams & Wilkins Company, 1928.  
Price, \$4.00.

THE first chapter treats in detail the phenomenon of precipitation, especially as it relates to the Kahn Test. There is a thorough discussion of the variants which lead to dissimilar results.

Incidentally the author does not prove the point that the complement fixing and the precipitin substances are identical, which he says is "in all likelihood" the case. His experiment merely indicates that

particulate matter will absorb complement, which fact is well recognized.

The succeeding chapters are essentially an elaboration upon the section on "Procedure" in "Serum Diagnosis of Syphilis by Precipitation," by the same author.

They deal with the several techniques for the Kahn test, as adapted to meet varying conditions, such as the routine test, the quantitative procedure with blood and with spinal fluid, and the micro procedures.

The author, in his paragraphs on clinical interpretation may show an overoptimism as to the reliability of the results of any single antigen method either of complement fixation or precipitation in syphilis.

There is a bibliography of 236 references to the literature since 1922. The chapters on the mechanism of precipitation are instructive and will be of interest to anyone employing precipitation methods, especially the Kahn test. F. L.

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WHAT IS LIFE? By AUGUSTA MASKELL. Pp. 324. Springfield, Illinois: Charles C. Thomas, 1928.

WHILE the authoress naturally does not conclusively answer her title question, she offers an interesting working hypothesis based on modern atomic physics. Her qualifications in the field of physics are vouched for in the introduction by Compton of Princeton; in the field of biology by Pearl of Johns Hopkins.

Almost half the text is devoted to a discussion of theories in general and of the presentation of one theory in particular and to preparatory statements about "the organism," "colloids," "matter" and "the atom," which are well worth reading for their own sakes by those not already possessing expert knowledge in modern physics. An extensive glossary makes the book intelligible to those even less adequately equipped in this regard.

The author's fundamental assumption is that protons and electrons are able to unite in combinations called "Z" systems, which, differing from ordinary elements in unknown ways, are the "active" constituents of living matter. As Professor Compton observes, our very ignorance of the nature of the ultimate particles of matter makes us admit at least the possibility of such a hypothesis. When it is said by competent persons to be applicable in various directions and submissible to experimental test in the physical laboratory, it should become of interest to all, even though the nature of the experiments to be tried were not outlined and were far from apparent to the reviewer. Let us hope that they will soon be forthcoming! Until then it is premature to consider that the subject has been advanced.

E. K.

SPASMOPHILIA. By EDWARD C. WRIGHTSMAN, M.D., formerly Clinical Assistant in Pediatrics, Northwestern University Medical School, Chicago. Pp. 155; 24 illustrations. Boston: Richard G. Badger, The Gorham Press, 1928.

THOUGH entitled Spasmophilia, this book is not a monograph, as only about one-fifth of the text is devoted to this subject. The remainder of the book concerns itself with infant feeding and with rickets.

It is designed for the general practitioner and is properly practical in nature and brief in discussion. The problems of infant feeding are considered with order and clarity.

It is disappointing to find the use of parathyroid hormone considered so vaguely and not to find some discussion of irradiated ergosterol. To others than the reviewer, the very informal style of the book may not detract from its dignity.

J. S.

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REPORT OF THE INTERNATIONAL CONFERENCE ON CANCER, London, July 17 to 20, 1928. Pp. 588. New York: William Wood & Co., 1928. Price, \$12.00.

THIS work is an encyclopedia on cancer. It is made up of a number of sections, the more important of which deal with the etiology, the relative values of surgery, radiation and chemotherapy in treatment, occupational cancer, sarcoma of bone, diagnostic methods, and the geographic and racial prevalence of cancer. The work contains much of the experimental, as well as clinical work, on cancer. The papers are on the whole extremely well written, the authors (Ewing, Murphy, Loeb, Miles, Lockhart-Mummery, Quick, Handley, Cheval, Lane-Claypon, Wood, Bang, Moynihan, Sprigg and many others) having been carefully selected. This book should prove most valuable to any one interested in the subject or any subdivision of it.

I. R.

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COLLOID CHEMISTRY, THEORETICAL AND APPLIED Vol. II. Biology and Medicine. By Selected International Contributors. Collected and Edited by JEROME ALEXANDER. Pp. 1029. New York: The Chemical Catalog Company, 1928. Price, \$15.50.

It is impossible in a brief review to give an adequate idea of the great range of subjects treated in this large volume of over a thousand pages, but it may be said that few of the more important applications of colloid chemistry to biology and medicine have been overlooked. As would be expected in a work prepared by over 50

separate authors (many of them acknowledged leaders in their respective fields), the treatment of the different aspects of the subject shows a certain lack of unity, which under the circumstances can scarcely be considered to be a fault. It might be wished that several of the contributions which fall decidedly below the scientific level of the remainder had been omitted and the space they occupy used for the extension of the sections contributed by such distinguished authorities as, for example, Sir William Bragg, Willstätter, Höber and E. B. Wilson. However, most readers will disregard these rather minor blemishes and will find in the volume an enormous amount of valuable and interesting material, much of it otherwise difficult to obtain.

M. J.

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**NEPHRITIS: ITS PROBLEMS AND TREATMENT.** By T. IZOD BENNETT, M.D., F.R.C. Physician with charge of outpatients, Middlesex Hospital, London. Pp. 94; 3 illustrations. London: Oxford University Press, 1929.

THIS book consists of the Goulstonian Lectures delivered before the Royal College of Physicians in 1928, in which the problems of uremia, of edema, and of hypertension were discussed, to which have been added chapters on the classification of nephritis and on treatment. Much recent work is presented with an extremely pleasant style, but the omission of important evidence (as for instance, the osmotic pressure of the plasma proteins in edema) renders the opinions expressed unconvincing.

J. H.

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**FOOD INFECTIONS AND FOOD INTOXICATIONS.** By SAMUEL REED DAMON, A.M., PH.D., Associate Professor of Bacteriology, Johns Hopkins University. Pp. 266; 33 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, \$4.00.

A DISCUSSION of the infections and the intoxications in which food plays an essential rôle in the transmission of the infectious agent or toxic material; it does not include food adulteration with chemicals, infectious disease due to chance consumption of inadvertently infected foodstuffs, diseases due to specific hypersensitiveness to certain foods, nor the avitaminoses. In Part I are considered the paratyphoid infections from food, tuberculosis from milk and meat, Malta fever from goats' milk (*Brucella melitensis*), septic sore throat from milk and actinomycosis. (The failure to refer to *Brucella abortus* infection from cows' milk is an important omission.) Part II deals with the food intoxications: botulism, mushroom poisoning, grain intoxications (ergotism, lathyrism), milk sickness, potato poisoning, fish and shellfish poisoning. Part III takes up the zoö-

parasitic infections acquired through food: trichinosis, tæniasis and others. The last two chapters having been written by Norman R. Stoll. While the author makes little claim of originality in the work, he has performed a most creditable task in gathering into this volume a great deal of material that heretofore could be found only by a laborious search in many textbooks, monographs and periodicals.

R. K.

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CLINICAL ELECTROCARDIOGRAMS. THEIR INTERPRETATION AND SIGNIFICANCE. By FREDERICK A. WILLIUS, B.S., M.D., M.S. in Medicine, Associate Professor of Medicine, The Mayo Foundation, University of Minnesota. Pp. 219; 368 illustrations. Philadelphia and London: W. B. Saunders Company, 1929. Price, \$8.00.

FROM the frequency with which books on this subject are appearing, it is safe to infer that electrocardiography is a good selling proposition in the medical book world—and at steadily rising prices! When Lewis' Clinical Electrocardiography was the only one in the field it sold for a modest sum; now that there are many—and surely all cannot be superlative—the price has risen to four, six and eight dollars. The margins are greater, to be sure, and the illustrations more spacious, but it is much to be doubted if there is a proportionate gain in value of the information extended.

Relieved of these strictures, the reviewer can conscientiously recommend the new book to those who wish to be led by easy stages through the steps of reading and evaluating clinically both typical and transitional records. Both illustrations and bibliography are liberally and well done.

E. K.

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SPINAL ANESTHESIA. By CHARLES H. EVANS, M.D. Pp. 203; 41 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$5.50.

THE author gives a survey of the literature on the general subject of spinal anesthesia and collects the available data, both clinical and experimental into a readily accessible form. He shows that spinal anesthesia is not only safe, when given understandingly, but that it is the most satisfactory type of anesthesia in a large group of cases. He quotes freely from his own wide experience as well as from the writings of Labat, Babcock, and others.

The technique which he recommends is based upon his own personal experience and data and in many instances he has added valuable points that enhance the value of this type of anesthesia which bids fair to replace all other forms in popularity.

The work is a very complete, concise and at the same time a comprehensive presentation of a valuable surgical handmaid. It is nicely written, judiciously illustrated and well edited. It is well worth ownership.

E. E.

**THYROXINE.** By EDWARD C. KENDALL, M.S., Ph.D.; D.Sc., The Mayo Foundation, Rochester, Minn. Pp. 265; 39 illustrations. New York: The Chemical Catalog Company, 1929. Price, \$5.50.

THIS is an excellent review of the physical, chemical and physiologic properties of thyroxine, prepared by one who is perhaps the foremost authority on the subject. It is published under the ægis of the American Chemical Society, as one of a series of scientific and technologic monographs. It is really more than a monograph, as it contains a comprehensive discussion of the normal and abnormal physiology of the thyroid gland, with some clinical applications. The style is smooth but concise; the literature has been thoroughly reviewed (there are 541 references) and the important contributions well summarized. The book constitutes the most authoritative single work extant on thyroxine and its relation to thyroid physiology, and belongs in the library of every clinician and physiologist.

E. R.

## BOOKS RECEIVED.

### NEW BOOKS.

*History of Blockley. A History of the Philadelphia General Hospital from its Inception, 1781-1928.\** By JOHN WELSH CROSKEY, M.D. Pp. 765; 15 illustrations. Philadelphia: F. A. Davis, Company, 1929. Price, \$10.00.

*Physical Therapeutic Technic.\** By FRANK BUTLER GRANGER, M.D. Pp. 417; 135 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$6.50.

*Die Menschenthymus in Gesundheit und Krankheit. II. Das Organ Unter Anormalen Körperverhältnissen.\** By J. AUGUST HAMMAR. Pp. 1114; 815 illustrations. Leipzig: Akademische Verlagsgesellschaft m.B.H., 1929.

*Four Centuries of Medical History in Canada.\** By JOHN J. HEAGERTY, M.D., D.P.H. Two volumes totaling pp. 769; 38 illustrations. Chicago: University of Chicago Press, 1928. Price, \$12.00.

*International Medical Annual for 1929.* Pp. 568; 160 illustrations. New York: William Wood & Co., 1929. Price, \$6.00.

A useful chronicle—mostly by British authors—for those who are satisfied with an annual attempt to keep up-to-date.

*Progressive Relaxation.\** By EDMUND JACOBSON, M.D. Pp. 429; 69 illustrations. Chicago: University of Chicago Press, 1929. Price, \$5.00.

\* Reviews of titles followed by an asterisk will appear in a later number.



*Diagnostic Methods and Interpretations in Internal Medicine.\** By SAMUEL A. LOEWENBERG, M.D., F.A.C.P. Pp. 1032; 547 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$10.00.

*The Mobilization of Ankylosed Joints by Arthroplasty.\** By W. RUSSELL MACAUSLAND, M.D. and ANDREW R. MACAUSLAND, M.D. Pp. 252; 154 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$4.00.

*A Patient's Manual of Diabetes.* By HERBERT W. MOXON, B.A. (CANTAB.), M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 132. New York: William Wood & Co., 1929. Price, \$2.25.

Written "with both eyes upon the patient," that is, not for the medical practitioner.

*A New Treatment of Cancer and Chronic Diseases.* By LA FOREST POTTER, M.D. Pp. 148. Boston: Richard G. Badger, 1929.

Not to be recommended, unless one expects profit from unsupported meanderings through the psychophysical treatment of the body, the electronic concept of human energy, and so on.

*Diseases and Deformities of the Spine and Thorax.\** By ARTHUR STEINDLER, M.D., F.A.C.S. Pp. 573; 76 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$12.50.

*Medicine. Its Contribution to Civilization.\** By EDWARD B. VEDDER, A.M., M.D., D.Sc., F.A.C.S. Pp. 398. Baltimore: Williams & Wilkins Company, 1929. Price, \$5.00.

*Old Age. The Major Involution.\** By ALDRED SCOTT WARTHIN, Ph.D., M.D., LL.D. Pp. 198; 29 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$3.00.

### NEW EDITIONS.

*Surgical Pathology.* By WILLIAM BOYD, M.D., M.R.C.P., Ed. Second edition. Pp. 933; 489 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$11.00.

An improvement on what was already a very good book. There have been extensive revisions and additions (including 130 new illustrations) so that the type was entirely reset. Many of the defects of the first edition (see this Journal, 1925, 169, 598) have been removed.

*Diseases of Children.\** Edited by SIR ARCHIBALD E. GARROD, the late FREDERICK E. BATTEN, HUGH THURSFIELD and DONALD PATERSON. Second edition. Pp. 1106; 205 illustrations. New York: William Wood & Co., 1929. Price, \$13.00.

*Diseases of the Nose, Throat and Ear.* By E. B. GLEASON, M.D., LL.D. Sixth edition. Pp. 617; 262 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$4.50.

*The Technic of Local Anesthesia.* By ARTHUR E. HERTZLER, A.M., M.D., Ph.D., LL.D. Fourth edition. Pp. 284; 146 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$6.00.

Emphasizing, like the previous editions, what operations can best be done under local anesthesia and the importance of the operator's skill.

*Laboratory Technique. The Methods Employed at St. Luke's Hospital, New York.* By F. C. WOOD, KARL VOGEL and L. W. FAMULENER. Third edition. Pp. 318. New York: James T. Dougherty, 1929.

This, or another as good, and I know of none better, should be on hand wherever hospital laboratory tests are being made. Reinforced by the larger books with explanatory and comparative data, they are most useful in giving concrete information when it must be had and quickly.

\* Reviews of titles followed by an asterisk will appear in a later number.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

W. S. THAYER, M.D.,

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AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

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**The Therapeutic Influence of the Reticulo-endothelial System.**—SAXL (*Wiener med. Wchnschr.*, 1927, 77, 865) points out that the reticulo-endothelial system (especially prominent in the spleen, lungs, bone marrow, Kupffer cells of the liver and the cutaneous connective system) is through its properties of phagocytosis an important agent in the purifying mechanism of the blood. It is also generally considered as the chief source of antibody production, as is shown by the fact that the antibodies are considerably reduced after proper blockage of the system or after splenectomy. If strain is put upon the reticulo-endothelial system its cells swell and reproduce rapidly, with many appearing in the blood stream. For instance, in subacute bacterial endocarditis many of these cells can be found laden with bacteria. The system is considered to be of great importance in intravenous therapy for many materials injected into the blood stream disappear from it quickly with deposition in the reticulo-endothelial system. Blockage of the system may be caused by hepatic stasis or sepsis or can be produced by injection of various substances, a procedure which may be of use in septicemia.

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**Quantitative Measurements of Pepsin in Gastric Juice before and after Histamin Stimulation.**—POLLARD and BLOOMFIELD (*J. Clin. Invest.*, 1929, 7, 57) precede their present publication with one on how to estimate quantitatively pepsin in the gastric secretion. Having given the method, they proceed to report the results of their analysis of gastric juice with the stomach at rest and after histamin stimulation. In the normal individual there was a concentration of chlorid and total output of chlorid after histamin stimulation, but concentration of nitrogen and of fixed base fell, although total output was somewhat

increased. Pepsin as found in the normal individual follows closely the curve of nitrogen concentration and falls markedly after histamin injection, although the total amount usually increases. This seems to be the most striking feature of the curves—the fall in the concentration of pepsin at the height of the secretion. In the abnormal cases, three in number, it was found that in a case of sprue, with free hydrochloric acid in the stomach, concentration of pepsin was lower than normal and did not show the typical drop after stimulation. A woman with pernicious anemia showed that in this disease, as observed in one patient, pepsin is still present in small amounts, but there is no relation between the nitrogen-pepsin curve. Likewise, in the gastric secretions of a man with advanced cancer of the stomach with a total absence of hydrochloric acid, pepsin was still present, though in small quantities.

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**Production of Colds with *Micrococcus Catarrhalis*.**—It has been suggested that a specific filterable virus is the etiologic factor responsible for colds. Ordinary bacteria are conceived to be merely secondary invaders. JOHN E. WALKER (*J. Infect. Dis.*, 1929, 44, 254) has held that the disorder is not due to a specific virus but a reaction is brought on by many different bacteria. As proof of his contention he has previously reported two accidental respiratory infections which brought about the signs and symptoms of the ordinary common cold. He now reports the deliberate production of colds in a volunteer by injections of *Micrococcus catarrhalis* sprayed into the nostrils of the subject. The following day the patient had sneezing, profuse watery discharge, fullness of the head and nasal obstruction. By the third day the discharge was somewhat purulent and the fourth day it almost disappeared. Nine days later the experiment was repeated without results; about three weeks afterward again, this time with a reproduction of the symptoms in experiment one. Infections due to *M. catarrhalis* are entirely similar to those produced by *B. influenzae* and *B. bronchisepticus*. It would seem then that bacteria such as are cultivated from nasal exudate are primarily responsible for the symptoms of the irritating, uncomfortable and disagreeable head cold.

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**Pernicious Anemia: Results of Treatment with Liver or its Derivatives in 67 Cases.**—Numerous reports have appeared in the literature in the past year on the effect of the so-called liver treatment of pernicious anemia. A report by WYMAN RICHARDSON (*New England J. Med.*, 1929, 200, 540) is of value because one may always be confident that the work emanating from the Massachusetts General Hospital is of the highest type and their reports may be accepted with absolute confidence. In the 67 cases of pernicious anemia which were followed from six to twenty-eight months, 6 of these patients have died, 5 dying from causes other than pernicious anemia and one from complicating toxemia. Four of the patients have varying degrees of central nervous system symptoms; one patient has carcinoma of the stomach. The remaining 56 patients are well. Richardson says that this series confirms in every way the striking beneficial effects of liver therapy for patients with this disease. It is quite possible by following months and years of treatment with an adequate liver intake to clear up the central nervous system

symptoms, but it is necessary to keep the red-cell count above 4,500,000 per cm. No one of their patients developed central nervous system symptoms during the course of their treatment. Measurements of the red-cell diameter were made in 11 cases, the median diameter returning to normal or below when the red-cell count attained normal figures.

**The Toxic Constituent of the Bile.**—It has long been known that bile is toxic, as proved by the lethal effects that occur when bile is injected intraperitoneally or flows into the peritoneal cavity when the gall bladder is ruptured. Various observers have attempted to define what is the toxic constituent of the bile. Some have held that it is the pigment, while others the bile salts, sodium glycocholate and sodium taurocholate. EMERSON (*J. Lab. and Clin. Med.*, 1929, 14, 635) has carried out a series of experiments with ox bile. Sodium glycocholate in a 3 per cent solution was injected into 10 dogs and sodium taurocholate in the same strength was similarly injected into 10 dogs. The pigment was obtained from human gall stones dissolved in alcohol and it, in turn, was likewise injected into the experimental animals. The lethal dose of whole bile averages 9.6 cc. per pound of body weight. The fatal dose of 3 per cent sodium glycocholate averaged 8.5 cc. and of sodium taurocholate 10.1 cc. The pigment solution was not able to produce any alteration of the blood pressure and respiratory rate, even up to 25 cc. per pound of body weight. It follows from these investigations that bile pigment is not toxic, whereas the bile salts, particularly sodium glycocholate, are the toxic constituents of the bile.

**Etiology of Acute Leukemias.**—There is considerable discussion as to the pathogenic factor responsible for the interesting condition of acute leukemia. In the present communication RUBNITZ (*J. Lab. and Clin. Med.*, 1929, 14, 497) has, as have most of the writers on the subject, advanced some hypotheses as to the causation of the disease. He discusses the possibility of the disorder being caused by a filterable virus. He mentions the possibility of leukemia being primarily a malignancy of the blood-forming tissues, and the last possibility is a special condition precipitated either by an infection or an abnormal metabolic state. The author, accepting the last theory, then defines leukemia as an unusual blood reaction to certain toxins. Because sloughing mucous membranes of the mouth are associated with the disease, the suggestion is advanced that the necrotic mucous membrane may contain a toxic substance which is the causative agent. He contrasts leukemia with Schultz's disease, in which there occurs a disappearance of the granulocytic elements from the blood stream and he assumes that the toxin in both agranulocytosis and acute leukemia is qualitatively the same and quantitatively varies. In agranulocytosis the lesion is active. The toxin is liberated in large quantities and the hematopoietic system is overwhelmed, whereas in acute leukemia less toxin is put forth and the blood-forming organs are stimulated to activity so that numerous immature cells are thrown into the circulation. Eventually the patient dies. As a result of these several hypotheses, Rubnitz believes that there is only one type of acute leukemia. The primordial cell may be a precursor of either the so-called myelocyte or large lymphocyte. The obscure toxin liberated by necrotic membranes is a leukocytolysin.

## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

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**Congenital Syphilis of the Thyroid Gland.**—MENNINGER (*Am. J. Syph.*, 1929, 13, 164) states that both hypothyroidism and hyperthyroidism occur with congenital syphilis and in some cases unquestionably are a part of the syphilitic process. Hypothyroidism is more frequent and probably results in most cases from the effect of an intrauterine toxin becoming manifest at an early age. Hyperthyroidism is more probably the result of a localization of infectious process to the gland and usually does not become evident before adolescence. Pathologically the thyroid may be increased several times in size, may be of normal size and even smaller. It is usually more firm and several authentic cases of gumma formation have been reported.

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**Blood-stream Infections in Urology.**—SCOTT (*J. Urology*, 1929, 21, 527) says that blood-stream infections occur much more frequently in urology than is generally supposed. Transitory infections or bacteremia, are much more common than the true septicemias. In 62 per cent of the cases presented in this study the blood-stream infections were postoperative in origin. The urethra was the probable portal of entry in 80 per cent of the cases. Seventy-seven per cent of the patients had bacillary and 23 per cent coccal infections of the blood stream. *Bacillus coli* was found most frequently occurring in 40 per cent of the cases. Death resulted in 18 per cent of the cases. In about 74 per cent of these, the infections were postoperative in origin and occurred for the most part in patients that were relatively poor operative risks. In the light of our present knowledge concerning blood-stream infections in urology the greatest hope from the standpoint of treatment is to be found in the field of preventive therapy. In the true cases of septicemia it is most important to locate and eliminate when possible, the primary focus of infection. In the presence of sepsis, pre- or postoperative, whether the blood cultures are positive or not, intravenous therapy may often be very helpful.

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**Fracture of the Carpal Scaphoid.**—GRACE (*Ann. Surg.*, 1929, 89, 33) claims that patients with fracture of the tubercle of the scaphoid obtain, as a rule, favorable results. Early recognition and adequate treatment offer the only chance for bony union in fracture of the body of the bone. Favorable results in fracture of the body of the scaphoid may be obtained in cases which are recognized and treated in the acute stage although bony union may not be obtained. The chronic cases are usually the unrecognized ones. Certain chronic cases, especially in people of sedentary occupations, have so little pain and disability that

they are best let alone. Chronic cases with persistent pain offer the best results to operation. Function or wrist power may not be improved in the chronic cases by operation. The patient's symptomatic or functional results cannot always be forecast by examination of the Roentgen ray in either the early or late cases.

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**The Blood Supply of the Thyroid Gland with Special Reference to the Vascular System of the Cretin Goiter.**—WANGENSTEEN (*Surg., Gynec. and Obst.*, 1929, 48, 613) says that the normal thyroid gland is provided with a more liberal and free source of arterial flow than is any other gland of its size in the body. In goiter the inferior thyroid artery is the larger but the more important vessel. Free anastomoses of all the chief arteries of the gland occur in the capsule. Anastomoses between the arteries within the gland itself, are thought not to exist, but a few such communications were observed on one corrosion specimen. The alteration in the disposition of the smaller bloodvessels, as goiter is intimately related to and dependent on the changes in the connective-tissue stroma in which the vessels run. In adenomatous goiter, where such changes are common, deviations from the normal size and distribution of the interlobular follicular and capillary vessels are frequent. In the goiter of the cretin, where degenerative changes are especially prevalent, transition from the normal arrangement of these smaller vessels is particularly likely to obtain. Degenerative changes in the vessel walls of arteries of all orders are common in adenomatous goiters. The large extra glandular vessels so frequently seen in cretin goiters represents a compensatory attempt to insure a good blood supply to a benign neoplastic process of a hypofunctioning tissue, in which the alterations in the stroma have made a normal nutrition impossible.

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**Stab Wounds of the Spinal Cord.**—RAND and PATTERSON (*Surg., Gynec. and Obst.*, 1929, 48, 652) believe that stab wounds penetrating the spinal cord are not infrequently seen in large emergency hospitals. The initial symptoms are often those of a complete cord lesion. In the majority of cases these symptoms change as time passes, usually becoming Brown-Sequard in type. The degree of recovery varies depending largely upon the extent of original cord injury. Laminectomy is indicated when a foreign body or bone fragments are present in the spinal canal. Lumbar puncture should be carried out to determine whether there is free blood in the spinal fluid or whether a block exists. Exploration will depend largely upon these findings. Cerebrospinal fluid leaks occasionally are seen and should be closed.

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**Extensive Resections of the Small Intestine.**—BRENIZER (*Ann. Surg.*, 1929, 89, 675) says that the arbitrary limit of assured safety, two meters applied to resections of the small intestines, is embraced in the term extensive. Resections up to and beyond the arbitrary limits have become necessary as life-saving measures and have yielded 85.7 per cent recoveries from operation, and 65.5 per cent good functional results. Functional recoveries in man, as in dogs, are likely dependent upon compensatory hypertrophy. Metabolic studies, both in animals and man, establish a diet rich in carbohydrates, less of protein but poor in fats.

## THERAPEUTICS

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UNDER THE CHARGE OF

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**The Treatment of Actinomycosis with Small Doses of Tincture of Iodin.**—CHITTY (*Brit. Med. J.*, 1929, i, 347) reports four cases of actinomycosis in which 5 minims of tincture of iodine administered thrice daily in milk or in cream exerted a curative effect.

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**The Conservative Treatment of Glaucoma.**—R. TIEL (*Therap. d. Gegenw.*, 1929, 70, 71) believes that in spite of the numerous claims for recently introduced therapeutic agents pilocarpin and eserine (physostigmine) is still the best drug for glaucoma. A 1 to 2 per cent solution of the pilocarpin and 0.25 to 0.50 per cent solution of the eserine is used. These drugs can be used without danger and change in the therapeutic efficiency for years. The usefulness of adrenalin is rather limited. In acute iritis with increased pressure and in glaucoma simplex it may be beneficial. It is not recommended in hemorrhagic glaucoma. Histamine is a more efficient myotic than pilocarpin or eserine (physostigmine). Among the substances which may act indirectly ergotamine, bromides, calcium, hypertonic salt and glucose solution may be of value. The secret of success is the individual treatment of the patient.

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**The Beneficial Effect of Vitamin D (Irradiated Ergosterol) in Osteomalacia of Adults.**—GOLDSTEIN (*Wien. klin. Wchnschr.*, 1929, 42, 202) refers to a number of cases of osteomalacia successfully treated with irradiated ergosterol. He reports observations on a male patient, aged sixty-five years, who for a number of years suffered from severe osteomalacia. The patient received vitamin D in form of "vigantol," 10 mg. daily and ultraviolet ray treatment. Distinct improvement was observed within two weeks. The dose of "vigantol" was then increased to 20 mg. daily. Almost four weeks after the beginning of the treatment the patient was able to walk.

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**Immunity Induced by Superficial Cutaneous Applications.**—LOWENSTEIN (*Wien. klin. Wchnschr.*, 1929, 42, 193) prepared a salve of diphtheria toxin and killed diphtheria bacilli. This salve was rubbed on the skin of about 400 children who were positive for the Schick test. Local or general reaction was not observed. Seventy per cent of these became "Schick negative." The examination of the sera for antitoxin titer indicated an increase in the antitoxin unit. The antitoxin formation lasts long after the application of the salve over the skin. From the observations it is clear that the human skin is capable of neutraliz-

ing considerable amount of diphtheria toxin. The significance of the skin as a source of immunity is underestimated at present. By rubbing the salve into the uninjured skin antitoxin formation can be produced. This can be demonstrated in the blood. High antitoxin values are reached within sixty days if the salve is rubbed in one to three times at intervals of fourteen days. This "salve method" is easily carried out and is entirely harmless. Investigations are in progress to study this method in other infectious diseases.

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**Malaria Treatment in Congenital Syphilis.**—KUNDRATITZ (*Therap. d. Gegenw.*, 1929, 70, 61) claims that a considerable number of patients with congenital lues are resistant to intense arsenical therapy. The author believes that in these children malaria treatment should be tried. The indications for malaria treatment are: (1) Involvement of the central nervous system; (2) patients with positive spinal fluid, even if symptom-free; (3) all cases with late manifestations, which are resistant to other specific treatments; (4) patients with positive blood serology, who fail to respond to other therapeutic measures. The malaria treatment in children is without danger. The youngest patient was three years of age. Contraindication of the treatment is organic heart disease, nonsyphilitic nephritis, active tuberculosis and severe anemia.

Three to 5 cc. of blood from a patient with malaria is injected subcutaneously or intramuscularly. After nine to fourteen days fever develops. The patient is allowed to develop 8 to 10 attacks of chills with fever, which is then stopped with 0.2 to 0.5 gm. of quinin administered twice daily for three days. Salvarsan treatment may be advisable following the malaria treatment.

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**Local Anesthesia in Operations for Hemorrhoids and Fissure of the Anus.**—BARBER (*Brit. Med. J.*, 1929, i, 396) states that local anesthesia for the operative treatment of hemorrhoids and fissure of the anus has many advantages over a general narcosis. A modified Reclus solution is used which consists of 0.5 cgs. of novocain, 1.6 cc. (24 minims) adrenalin (1 to 1000) and 100 cc. of physiologic saline solution. The injections must be well spaced so that considerable extent of the subcutaneous tissue is infiltrated. After preparation the patient is put in the lithotomy position. (1) About six pledgets of cottonwool are first prepared, their diameter being that of the little finger and their length 1 inch. They are tied in the middle with a piece of silk or linen thread to be used as a tractor for removal. The pledgets are soaked in 15 to 20 cc. of the solution and are introduced into the anus, while the patient "bears down." (2) The anus and the surrounding skin is rubbed with iodine. (3) Six to eight injections are made then along the junction of the skin and mucous membrane, so as to encircle the anus. The total amount of solution used is 30 to 40 cc. (4) The pledgets are removed. (5) The forefinger of the left hand is inserted into the rectum, and after the internal sphincter is hooked it is drawn down. (6) The sphincter is encircled with six to seven injections equal to 30 to 35 cc. of the solution. Insensibility is now complete. This method of anesthesia was used by the author since 1910 without a complication or a single slough. The extra time required is richly compensated by the good results.



**The Treatment of Malaria with Plasmochin.**—Plasmochin was used in the treatment of malaria on 100 patients by NISSENBAUM (*Wein. klin. Wchnschr.*, 1929, 42, 300). A dose of 0.15 gm. of plasmochin, used originally, was abandoned because it frequently produced severe cyanosis. Doses of 0.06 to 0.1 gm. administered daily were effective. Such amounts were given for five days, followed then by a period of one week without drug therapy. The duration of the treatment was six to seven weeks. Cyanosis was occasionally observed as a complication, due to the presence of methemoglobin. Diarrhea and generalized aches also developed in a few cases. The presence of jaundice does not contraindicate the use of plasmochin. The author believes that plasmochin is an effective agent in the treatment of malaria, especially in the tertian and quartan types. Remissions are apt to occur less frequently after plasmochin than after quinin. In tropical malaria, plasmochin should be given together with quinin, thereby preventing the development of gametes. Plasmochin is the first known preparation capable of destroying the gametes of tropical malaria. In cases of quinin idiosyncrasy, quinin resistant malaria, and pregnancy, plasmochin may efficiently replace quinin.

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## PEDIATRICS

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UNDER THE CHARGE OF

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**The Premature Infant.—Clinical and Pathological Study.**—CLEIN (*Am. J. Dis. Child.*, 1929, 37, 751) studied 102 infants. Clinically he found that cyanosis in premature infants is the most important symptom and is of great diagnostic and prognostic value. The graver pathologic process, such as infratentorial hemorrhage, atelectasis and infections, can often be diagnosed on the type of cyanosis. He presents a tentative classification as follows: (1) continuous cyanosis which is most often due to atelectasis; (2) intermittent cyanosis occurring during the first few days which is usually the result of infratentorial hemorrhage; (3) antemortem attacks often occurring in infants dying of infection, and (4) sporadic cyanosis for which some other cause can often be seen at the time of the attack. He found that severe diarrhea may occur as a complication secondary to systemic or focal infection more often as a primary condition in breast-fed babies. Jaundice may occur in severe form after the first week usually as a symptom of infection and sepsis and which may be associated with intracranial hemorrhage. Vomiting of a severe type is often associated with sepsis and infection. Distention is a frequent symptom in association with these conditions. Besides these, there are no other symptoms that are regularly of any definite diagnostic and prognostic value. Signs of increased intracranial pressure such as bulging fontanelles, convulsions and twitching are infrequently seen in premature babies having intracranial hemorrhage although these symptoms may occur. Elevation of temperature was noted in about one-third of the infants having infections while sub-

normal temperatures are frequently seen. Although infections occur in many forms, otitis media is the most frequently met and pneumonia is the most fatal infection. From the pathologic standpoint, he found that certain pathologic lesions produced a constant symptom complex in the infant. Other pathologic lesions in the same infant did not seem to cause any regular symptoms. Infratentorial hemorrhage invariably caused intermittent cyanotic attacks. Among the lesions which did not as a rule produce definite symptoms were cortical hemorrhage, moderate degree of atelectasis, patent foramen ovale and ductus arteriosus and mild infections. Atelectasis and infratentorial hemorrhage affected chiefly the most immature infants and usually caused death within the first three days. Acquired infections occurred in older and heavier infants usually after the first two weeks of life. Those with tuberculosis and syphilis were older and heavier, and died at a later age than the infants in other groups. The newborn infants that were admitted and died within the first or second days showed definite signs of immaturity of tissues and organs and the usual cause of death was intracranial hemorrhage and atelectasis.

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**Cisterna Puncture during Childhood.**—FANCONI (*Schweiz. med. Wchnschr.*, 1929, 59, 149) prefers in some cases the cisterna puncture to the lumbar puncture. He has done or seen done a very large number of these operations without observing any serious consequences. He feels that a cisterna puncture should be made when an exact examination of the cerebral spinal fluid is necessary because the fluid obtained by this method is less often mixed with blood than that obtained by the lumbar puncture. If diagnosis requires the withdrawal of fluid and if lumbar puncture fails to give the desired results, cisterna puncture should be employed. Cisterna puncture is also indicated in cases of high intracranial pressure, especially in presence of cerebral tumors. In cases of glioma of the cerebellum, which occur with some frequency during childhood, cisterna puncture is less dangerous than lumbar puncture. The difference in pressure which is caused by lumbar puncture frequently forces parts of the cerebellum into the foramen magnum and in this manner gives rise to symptoms of compression. Cisterna puncture is of advantage in encephalography because it permits the introduction of air directly into the ventricles of the brain. The ideal posture for the patient in cisterna puncture is to be lying horizontally with the head slightly turned.

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**The Healthy Carrier in Scarlet Fever.**—TUNNICLIFF and CROOKS (*J. Am. Med. Assn.*, 1929, 92, 1498) use one method to detect the healthy individuals who are carriers of scarlet fever. They heat normal and immune horse serum at 56° C. for one half-hour to get rid of normal opsonins. For the serums containing antiseptics it is necessary to dilute them 1 to 10 with salt solution on account of the inhibited actions of the antiseptics on phagocytosis. Equal parts of normal human or guinea pig blood and 2 per cent sodium citrate in salt solution are mixed. Three large drops of blood is sufficient for 12 specimens. Whole blood instead of washed leukocytes has the advantage of containing fresh serum which activates the opsonins in the immune serum if that serum has not been recently collected. The citrated blood should be

used soon after it is collected. Streptococci on the original blood agar plate or from twenty-four-hour subcultures are suspended in salt solution. Thick suspension should be avoided in order not to get too much phagocytosis for accurate counts. Equal parts of serum, citrated blood and bacterial suspension are mixed in bent capillary pipets and the mixtures are incubated for twenty-five minutes at 36° C. then smeared on glass slides and stained. Fifty or more polymorphonuclear leukocytes are counted and the number of cells showing phagocytosis is noted. This latter is the phagocytic index. If the phagocytic index of the immune serum exceeds that of normal serum determined by the same method, the coccus belongs to the scarlet fever group. Usually the differences between the normal and the immune specimens should be marked. The opsonic indexes with the scarlatinal streptococci from the carriers in the series studied vary from 4 to 18. The authors were able to discover three healthy carriers of scarlet fever streptococci from whom 14 cases of scarlet fever had developed.

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**Heart Disease in School Children.**—CAHAN (*J. Am. Med. Assn.*, 1929, 92, 1576) analyzed the examination of the hearts of 10,333 children in 10 public schools with an aggregate school population of 11,578 pupils. The general incidence of organic heart disease was 0.91 per cent. The younger children had a slightly lower incidence of heart disease than the older pupils and the occurrence in boys was slightly less than that in girls. The most common lesion found was mitral stenosis. This diagnosis was made in 53 of the 94 children suffering with heart disease as found in this survey. Fourteen of these 53 showed the combined lesion of mitral insufficiency with the mitral stenosis. The children with cardiac lesions were grouped under three general headings: (1) those with severe heart lesions unable to attend any school; (2) those with crippled hearts attending special classes; (3) those with definite or suspicious lesions. It was found that the examinations made without undressing the chest were inadequate. As the result of the experience of this study it was felt that school physicians would make a more complete examination and improve the diagnosis and overlook fewer heart conditions if the exposure of the entire chest was introduced in the school examinations.

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**The Prophylaxis of Measles.**—LEINER (*Wien. klin. Wchnschr.*, 1929, 42, 295) discusses various methods for the prophylaxis of measles. He feels that the Degkwitz method is the most effective. On two occasions this has been used in the childrens' hospitals when a child with measles was brought in. In both instances, all the children were given the prophylaxis injection and an epidemic was prevented. The serum should be taken from patients with measles during the period of convalescence. In experiments made with the serum from animals, effective results were not secured. When it is difficult to secure a sufficient quantity of convalescent serum, serum or blood from adults who have had measles may be injected. He found that this was effective in about 50 per cent of the cases. This method requires a larger quantity than convalescent serum. He especially recommends this method for infants, for children with rickets, tuberculosis or other diseases and especially to prevent measles in childrens' homes and hospitals.

## DERMATOLOGY AND SYPHILIS

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**Summer Shortening of Incubation Time in Malarial Inoculation of Syphilis Patients.**—HECHT-ELEDA (*Arch. f. Derm. u. Syph.*, 1928, 156, 377) found that the incubation period of inoculation malaria in a series of 170 patients fell from seven days in winter to four to five days in summer. It is accordingly concluded that the optimum period for a "take" is the summer months.

**A Case of Chronic Relapsing Pseudodiphtheria of the Skin, Simulating Late Syphilis.**—HARTMAN (*Arch. f. Derm. u. Syph.*, 1928, 156, 126) describes as a rare condition, a case of recurrent, refractory ulcerative and destructive lesions of the scalp, skull, skin and deeper tissues, regarded and treated for five years as malignant syphilis. The attacks lasted from six to nine months with three-to-six-month intervals. Deep necroses of scalp and skull with sequestra, large ulcers with curious linear scars as sequels, and an absence of membrane formation were noted. Papulonecrotic lesions developed on the face, which, in the illustration, suggest anthrax lesions. A pseudodiphtheria strain, of which the woman was a carrier in both nasal and genital tracts, was isolated from the lesions and agglutinated by patient's serum in a dilution of 1 to 32,000. No toxins were produced in culture. No ulcers could be reproduced in animals. Sachs has reported 3 similar cases.

**On Reinfection with Experimental Syphilis, with Regard to the Quantity of the Spirochetes Used for Inoculation.**—HONDA (*Acta Dermat.*, 1928, 12, 607) states that reinoculation experiments were conducted on 16 untreated syphilitic rabbits which had been infected more than one hundred days before. For the first infection the virus strains Nos. H. and F. were introduced testicularly or scrotally, with the appearance of the typical local lesion. After one hundred and twenty-five to nine hundred and eighteen days had elapsed following infection, the animals, many of which had no visible lesions, were reinoculated with syphilitic orchitic tissue introduced in the scrotum while the other scrotum was inoculated with virus emulsion through a scarified area. Controls were treated in the same way. All the reinoculated animals developed a lesion in the scrotal area, while in 3 cases scrotal chancre was produced at the site of the tissue implantation.

**A Clinical and Biochemical Study of Allergy.**—BARBER and ORIEL, (*Lancet*, 1928, ii, 1009; Part II, ii, 1064) include in their group the Besnier prurigo-asthma-hayfever-ichthyosis syndrome. They point out the common denominator of a sensitization etiology and a marked nervous background. They define their conception of prurigo (Besnier) in the terms of Rasch to include a familial allergy, onset early in childhood, the involvement of the face neck and flexures, the intense pruritis with nocturnal exacerbations, the nervous pale restless child, the eruption chronic and resistant in course, coincidental asthma or (in adults) light sensitization, and the therapeutic effect of a strict lacto-vegetarian diet. They noticed in common with others the beneficial effect of climatic and domiciliary change on the pruritus. The entire picture rests in their opinion on a vegetative nervous-system foundation. Biochemical investigations were carried out on the blood and urine of these patients and the authors found that the average amino-acid content of the blood was raised from a normal figure of 4 to 6.5 mg. per 100 cc. to 8.8 mg. per 100 cc. Urticarial patients gave a similar but somewhat lower elevation (average of 7.8 mg.). A moderate response was noted in cases of light sensitization and dermatitis herpetiformis. The normal whole-blood chloride figures of 454 to 495 mg. showed a constant reduction in acute and chronic asthma-prurigo to an average figure of 400. The serum chlorides were reduced slightly if at all, the main reduction therefore being in the corpuscular content. An explanation comparable to that given for similar figures is obtained in experimental high intestinal obstruction. The symptoms of toxemia are due to the absorption of the proteoses by the damaged intestinal mucosa and the utilization of the chlorides to neutralize the toxic substances. The authors found that in the period just preceding and during the paroxysms in the allergic conditions under study the free acidity of the urine rises and urates are often deposited on cooling. The urinary excretion is diminished and the specific gravity is usually increased. There is a retention of chlorids and a positive ether reaction. (A test described by the authors and formerly used in cardiac failure with edema, in which a few drops of 25 per cent sulphuric acid is added to 2 cc. of urine in a test-tube followed by a half-inch layer of ether. The mixture is shaken and a positive result is the appearance of a viscid and opaque layer at the ether-urine junction.) The ammonia excretion rises and the ratio of free acid to ammonia-combined-acid is altered. Finally, the excretion of amino-acid, creatinin, and uric acid begins to rise. In the period following the subsidence of the paroxysm the urine shows a rapid and progressive fall in free acidity to neutrality and finally alkalinity. The volume of urine excreted is raised and the specific gravity falls. The excretion of chlorids is increased and the ether reaction diminishes or disappears. The excretion of ammonia falls with a still further disturbance of the ammonia and ammonia-combined-acid ratio. Finally, there is a gradual drop in the excretion of amino-acids, creatinine, and uric acid. The van den Bergh reaction when positive in these patients is of the biphasic type. In the light of their findings the authors have outlined a rationalized scheme of treatment to include a lacto-vegetarian diet, the administration of aromatic spirits of ammonia in small amounts before meals, ephedrin to those patients clinically showing exhaustion of the adrenals, and glucose daily 2 to 4 ounces in divided doses.

## GYNECOLOGY AND OBSTETRICS

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**Operative Treatment of Uterine Myomata.**—From the clinic of Kiparsky, in Leningrad, comes a report on the operative treatment of 510 uterine myomata which has been presented by MANDELSTAMM (*Zentralbl. f. Gynäk.*, 1928, 52, 2760). There were 384 abdominal operations with a total mortality of 2 per cent. These cases are subdivided into 101 complete hysterectomies with a mortality of 2 per cent, 221 supravaginal hysterectomies with a mortality of 1.8 per cent and 62 myomectomies with a mortality of 3.2 per cent. There were 126 patients treated by vaginal operations, such as complete hysterectomy, supravaginal hysterectomy and myomectomy with a total mortality of 1 per cent. He states that there should be no operation of choice in the treatment of myoma, but that each case should be decided on its own merits and be subjected to the proper operation. Myomectomy should be performed in young women whenever possible. Complete hysterectomy is indicated when there is a complicating carcinoma of the cervix or cervical myoma, in the presence of inflammatory disease of the cervix or when the cervix is fixed on account of posterior parametritis causing pain, in the presence of secondary changes in the tumor, such as necrosis, suppuration or malignant degeneration and in any cases in which the pouch of Douglas must be drained. In all other cases supravaginal hysterectomy should be preferred.

**Radical Operation for Cancer of the Cervix.**—The operative treatment of cancer of the cervix is employed in such a comparatively few clinics in this country at the present time, that in order to know what is going on in this field we must investigate the clinics of Europe. In a very interesting report of the work he has done in Leipzig and Berlin, STROECKEL (*Zentralbl. f. Gynäk.*, 1928, 52, 39) presents a series of 206 cases in which he performed the radical operation by the vaginal route with a primary mortality of 4.8 per cent. He employs the vaginal route because he believes that the parametrial tissues can be removed more completely by this method. He has been able to show a four-year cure in approximately 50 per cent of the cases which, of course, is as good as can be shown by the abdominal operation and, in addition, the primary mortality by the vaginal route has been much less. There were several cases of injury and also secondary necrosis of the neighboring structures, such as ureter, bladder and rectum, but in the majority

of the cases these injuries healed spontaneously. While the original article is too detailed to lend itself to satisfactory abstracting, it is mentioned here to remind the gynecologists in this country that radical operations are still being done in large numbers in certain foreign clinics.

**Treatment of Gonorrhea in Women by Diathermy.**—In order to obtain an idea of the value of diathermy in the treatment of gonorrhea in women, PUGH (*Phys. Therap.*, 1928, 46, 32) collected 500 cases including 200 cases of his own which had been subjected to this form of treatment and in which there were complete notes of the progress of the cases. In this group the apparent bacteriological and clinical cures are about 70 per cent, the vast majority of which were acute cases. In about 10 per cent of the cases the patients could not tolerate diathermy in the urethra. As a result of his study as well as his personal experience he believes that diathermy is an ideal method of treatment of gonorrheal infection of the urethra and cervix but must always be handled by a physician and not by a technician. If carefully given, it is usually painless. From the standpoint of secrecy, it is ideal in that the patient does not have to have a douche bag or medicines about her room. For best results the treatments should be given about twice a week and continued until five negative smears are obtained.

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF

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**A Classification of Deafness Based on the Effect of Deafness on Efficiency in Life.**—Asserting that deafness being only a symptom, a classification may begin from several points—as its cause, its degree, its effect on the deafened person, and so forth; that any classification starting from one point will cut across or overlap any other starting from any other point; and that “any classification of the deaf worth talking about must have more than an academic value,” LOVE (*J. Laryngol. and Otol.*, 1929, 44, 78) puts deafened children into four main groups—A, deaf mute; B, “muted or semimuted;” C, speaking deaf; D, partially deaf, hard of hearing, and semideaf. Those in class A are due to “congenital defect in development”—either Mendelian or hereditary syphilis (few). In classes B and C, cerebrospinal fever and hereditary syphilis are responsible for the deafness, which occurs later in child life in Class C. Members of B and C are totally deaf. Children in the three groups are incurable and must be educated in special schools for the deaf, which applies also to the severer cases in Class D, due chiefly to middle-ear disease, rather than to nerve deafness as seen in Classes B and C. Class D is the largest group and the hearing of many in this group can be improved. Love doubts that syphilis is a common cause

of congenital deafness. In concluding, he indicates four practical measures to decrease the inefficiency of these sufferers: (1) An intensive campaign against diseases of the ear in children; (2) an intensive study of sclerosis with a view to its prevention; (3) compulsory notification of syphilis; (4) training of the public in the causation of congenital deafness, to discourage intermarrying of the congenitally deaf and their relatives.

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**The Bacteriology and Clinical Course of Acute Suppurative Otitis Media, Acute Mastoiditis and their Complications.**—From observations made on a series of 275 patients, HESSE (*Ztschr. f. Hals.- Nasen.- Ohrenh.*, 1929, 22, 372) is convinced that predisposition to the occurrence and spread of suppurative lesions of the middle ear and the mastoid cells depends to a large extent on both constitutional and anatomic factors. In emphasizing that resistance of the host plays a more important rôle than virulence of the invading microorganisms in determining the gravity of the infection, he discusses the relative value of several immunologic procedures in estimating each of these factors. Those cases due to *Streptococcus mucosus* (*Pneumococcus* III) were particularly severe in adults. The author states that the source or prognosis of a given infection of the tympanic cavity and its sequelæ can be determined only by evaluation of all the various factors collectively and not individually. Such influencing factors as type and virulence of the causative bacteria, the hematologic and serologic findings of the patient and the local anatomic and pathologic conditions as revealed by Roentgen ray or encountered at operation are stressed by Hesse.

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**Dental Caries in Paranasal Sinus Infections.**—Although able authorities have taught that 20 per cent of maxillary sinus infections are of dental origin. BERRY (*Arch. Otolaryngol.*, 1928, 8, 698) after a careful examination of 152 patients, believes that 60, and perhaps 80, per cent would be a more accurate estimate of the dental complications in maxillary sinusitis. Of these, 18 per cent were of "proved," 30 per cent were of "probable," and 41 per cent were of "possible," dental origin. After a consideration of the anatomic and pathologic factors, the author stresses the value of transillumination of the alveolar process, as well as of the sinuses, by the instrument commonly employed by dentists. The electric vitality test and Roentgen ray were other important methods of examination. He contends that relatively prompt discharge of alveolar infection into the antrum stops the bony resorption which one looks for in the radiographs; and that in this type of case, unless new methods for diagnosis become available, it is the rhinologist, working with the dentist and the roentgenologist, who will determine whether harm is resulting.

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**Roentgenologic Signs which Indicate Extension of Infection from the Ethmoid and Sphenoid Sinuses to the Base of the Skull.**—By placing the top of the head downward on a Potter-Bucky diaphragm so as to bring the base of the skull as nearly parallel to the film as possible, and by directing the central ray through the larynx toward the vertex of the skull, PFÄHLER (*Arch. Otolaryngol.*, 1928, 8, 638) frequently has



demonstrated the extension of chronic deep sinusitis (ethmoids and sphenoids) to the base of the skull. This extension is characterized by a local or general osteitis, as indicated by increased density due to increased lime deposit, which probably is the result of a reaction of the inflamed dura mater. The extension may affect any of the fossæ of the skull, on either or both sides. Certain deformities or anomalies of the sella turcica and its attachments may be due to an extension of this inflammatory process.

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**How and when the Mucous Membrane of the Maxillary Sinus Regenerates. An Experimental Study in the Dog.**—To determine what histologic changes occur after removal of the lining of the maxillary sinus, KNOWLTON, assisted by MCGREGOR (*Arch. Otolaryngol.*, 1928, 8, 647) denuded at operation an antrum of three dogs and observed the histologic picture at varying intervals afterward. It was seen that one month after the antral lining had been removed, epithelial regeneration was well established and bone formation had begun; that three months after operation, epithelial regeneration was complete and the canine fossa opening was nearly filled in with bone; and that five months afterward, gland regeneration was well established, and the mucoperiosteum as a whole looked almost normal. Human antral sections indicated that the same processes occur in man.

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**Apparatus for the Quantitative Testing of Air and Bone Transmitted Speech.**—The usual test for the relative acuity of hearing air and bone transmitted sound is made with a series of tuning forks. It is well known that the greatest disability of the deafened person consists in his inability to hear conversations. As the sounds from the tuning fork are comparatively pure tones, while the voice sounds are complicated combinations of tones, the fork tests are a poor criterion of the sensitivity of speech. POHLMAN (*Proc. Soc. Exper. Biol. and Med.*, 1929, 26, 355) calls attention to a quantitative method of producing voice sounds in the phonograph audiometer with its electromagnetic pick-up. The instrument may also be used with a bone telephone by stepping up the energy with a two-stage audio-amplifier. As it is possible to test both air and bone acuity with the same receiver under the same mechanical conditions, a direct comparison can be determined. After briefly outlining the technique of examination and stressing the obvious advantage of employing a single receiver to ascertain both air and bone acuity, the author indicates other desirable features of the procedure.

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**Relation of Otolaryngologic Disease to Mental Disease.**—After a general discussion of his subject. FREE (*Arch. Otolaryngol.*, 1928, 8, 707) concludes that a definite and dependable relationship exists between physical disease and abnormal mental functioning; that in mental diseases, infections of the nose, throat and paranasal sinuses frequently form a part of the symptom complex; and that diagnosis and treatment in early cases may prevent the development of a psychosis and in patients already hospitalized contribute to their comfort, and sometimes to their cure.

## RADIOLOGY

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**Radiotherapy in Chronic Myelogenous Leukemia.**—According to LEDDY (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 250) myelogenous leukemia, like the other lymphoblastomas, is generally fatal from two to three years in spite of any form of treatment. Radiotherapy will produce remissions in at least 50 per cent of cases for an indefinite period, even to the point of freedom from symptoms. The treatment is best started with slow irradiation of the spleen and the body generally. High doses of radium and Roentgen rays are better reserved for the inevitable stage of refractoriness.

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**Studies of the Thymus.**—PERKINS (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 256) states that whether or not a child presents clinical symptoms of status lymphaticus, the finding of an enlarged shadow in the mediastinum, not characteristic of some other lesion, should be a warning of potential danger when either a major or minor surgical operation is considered. Observations at the Seaside Hospital indicate that between the ages of one and seven years 8.6 per cent of all children exhibit mediastinal shadows characteristic of thymic enlargement.

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**Treatment of the Thymus.**—From their observations, KINNEY and TAYLOR (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 263) have been led to believe that in the newborn attacks of cyanosis with or without dyspnea, or attacks of extreme pallor with flaccidity are more often associated with enlarged thymus or atelectasis than with all other causes combined, and that in the majority of cases the offender is the thymic gland. In a series of 213 children given Roentgen therapy, no fixed relation between the symptoms and the size, shape or density of the upper mediastinal shadow could be determined. Of the 213 patients treated, 7 had a return of the gland shadow unaccompanied by a return of symptoms; 13 had a return of both shadow and symptoms with the disappearance of both after a repetition of the therapy.

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**Bone Changes in Leprosy.**—Bone changes are usually marked in both types of leprosy, whether of the skin or nerves, writes HOPKINS (*Radiology*, 1928, 11, 470). The most marked osseous change takes place in the phalanges of the extremities and the nasal septum, while the bones of the trunk and the long bones of the legs and arms are untouched. The actual loss of bones causes a mutilation of the hands and feet, which is so characteristic of leprosy, and may be absorption

of bone without any evidence whatsoever of inflammation or suppuration of the overlying tissues. Bone loss is followed by retraction of the soft tissues, the tips of the finger nails often projecting from the phalanges when the digit has disappeared. The absorption of the nasal septum is followed by the sinking in of the soft parts of the nose. This process of bone absorption is usually a very slow one. Ten, twenty or thirty years may elapse while the digits are gradually shortening. When suppuration occurs, of course, it is much more rapid.

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**Roentgen Diagnosis and Treatment of Enlarged Symptomless Thymus.**—O'BRIEN (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 271) assumes that the 6 or 7 per cent of cases of "broadened mediastinal shadow" seen in children without symptoms represent at least relatively enlarged thymus glands. No one who is informed thinks for a moment that all of this group represent pathologic glands. The group undoubtedly comprises glands which have not undergone accidental involution from disease, those in which the rate of chest growth has not kept pace with the thymus, as well as those glands considered potentially a menace. Since it is known that involution of the thymus takes place rapidly and without harm (Hammar) following Roentgen or radium treatment, it would appear not only desirable but requisite to prescribe radiation therapy for children presenting a "broadened mediastinal shadow" without symptoms, if general anesthesia or surgery is contemplated.

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**Ossification of the Costal Cartilages in Relation to Habitus and Disease.**—Ossification in the costal cartilages was analyzed by RIEBEL (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 44) in 341 cases and correlated with the incidence of tuberculosis, syphilis and habitus. The finding of Rist Gally and Trocme that ossification proceeds more rapidly in the male was confirmed. No relationship with tuberculosis, either as an etiologic factor or as a result, could be discerned; this is contrary to the findings of certain German authors, who consider early ossification as a cause of tuberculosis and also as a feature of favorable prognostic import. No relationship to habitus was discovered. Extensive ossification appeared to be more frequent in syphilitic patients, particularly in the upper decades of life. However, the very wide range in the stages of ossification which can be discerned in any age group makes this sign of very limited value in the individual case.

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**Roentgen-anatomical Studies of the Colon in Tuberculous Patients.**—Three hundred tuberculous patients were examined by SAMPSON and HALPERT (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 37) to determine whether the colon has any roentgenologic characteristics peculiar to tuberculous persons. The cecum was found on the linea terminalis in 50 per cent of the males and 47 per cent of the females, and in the pelvis minor in about 23 per cent of the males and about 43 per cent of the females. The hepatic flexure was an acute angle and the first portion of the transverse colon lay parallel with the ascending colon for half the length or less of the ascending colon in about 41 per cent of the males and 30 per cent of the females; the first part of the transverse colon lay

along the ascending colon for more than half its length in 22 per cent of males and 35 per cent of females. In all but 3 males and 2 females the transverse colon was at a lower level than the greater curvature of the stomach.

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**Iodized Oil in Roentgenology.**—Iodized oil, whether used as lipiodol or iodopin, in commercial strength or diluted, is an excellent opaque medium for roentgenologic examination, in the opinion of FRIEDMAN (*Radiology*, 1929, 12, 114). Injections of the oil are harmless in the nasal accessory sinuses, Eustachian tubes and lachrymal ducts. Exploration of the bronchial tree is comparatively free from danger but cases must be selected; it is contraindicated in tuberculosis and hyperthyroidism. Injection of the oil into the renal tract is inexpedient; sodium iodid solutions are better. It is valuable and harmless in examining the uterus. Meningeal examinations must be made with caution.

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**The Inverted Cecum.**—Inversion of the cecum, a condition in which the cecum is folded upward on the ascending colon, is probably more common than is generally supposed, according to FRIED (*Am. J. Roent. and Rad. Therap.*, 1928, 20, 531). The malposition is congenital. In the cases reported by Fried it was characterized clinically by attacks of abdominal pain which was sometimes relieved and sometimes aggravated by changes of posture. Usually the pain was relieved by standing. In two cases there was tenderness over the right iliac fossa and appendicitis was diagnosed. On roentgenologic examination with a barium enema the inversion was manifest in each case. It was noteworthy that when the patient assumed a standing posture the cecum frequently turned downward into its normal position.

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**Radium Therapy of Cancer at the Radium Institute of Paris.**—REGAUD (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 1) holds that radium therapy through natural cavities of the body cures with regularity only epidermoid carcinoma of the cervix uteri, and only when the cancers has not as yet extended far beyond the limits of the uterus. In cancers which are more extensive this procedure can be used only as an addition to irradiation from an external source. In other localizations of cancer intracavitary radium therapy usually results in only temporary diminution of the tumor. The only cancers which have been cured, as a rule, by radium therapy are cancers originating from epidermoid structures. Adenocarcinomas are in general more radioresistant. At the Radium Institute in Paris they have been unable to cure by radiotherapy, adenocarcinomas of the rectum or cervix uteri except in a few rare instances. Direct cytolethal action of radiation is the essential phenomenon in the treatment of cancer; variations in the number of leukocytes and lesions in the vascular and connective tissues are inconstant and late. Gamma rays of radium have an undoubted biologic superiority over our present day Roentgen rays. This superiority results from a selective action which is especially defined in its biologic effects on sensitive cells. Nevertheless, it is possible that the inferiority of Roentgen rays is only temporary and that increase in their penetration power will reverse this relation.

## NEUROLOGY AND PSYCHIATRY

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UNDER THE CHARGE OF

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**The Freeing of the Teacher.**—HARDY (*Ment. Hyg.*, 1929, 13, 33) states that the traditional teacher was considered good on the basis of her respect for authority, impersonal interest in either method or subject matter and the possession "as a right and a glory" of the power of authority. "In all these qualities it would seem to me that our general systems of education, children of the nineteenth century, have reflected the tendency of the nineteenth century to recognize and respect only what could be formulated in words or measured in figures. The spirit of man, whether in the teacher or in the child to be taught, since it cannot be formulated, has not been honored. The new education has arisen from the needs of the spirit, calling for the restoration of what it has lost." She believes that the only method available at present for the selection of teachers for the purpose of advancing the new pedagogic principles is that of impression on the part of the employing body. To offset this she would have a continuation of the present efforts to establish standard scored tests of personality and other tests of judgment in concrete situations. In order to produce the type of individual needed for teaching purposes she would seek to revise all the training-school schedules.

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**Sodium Bromid Therapy in Functional and Organic Psychoses.**—BLACK (*Psychiatric Quarterly*, 1929, 3, 49) reports the results of intensive use of bromides in functional and organic cases at the Utica State Hospital since June, 1924. He states that bromides were administered to these cases up to the point of intoxication. Doses ranged from 60 to 240 grains a day for varying periods of time, the object being to induce bromid intoxication. He calls attention to the fact that bromide rash appeared in only 10 of the 86 cases treated, in spite of the other symptoms of intoxication and that when this symptom occurred it responded immediately to treatment with Fowler's solution. In half of the cases the bromid dosage was diminished during the rash and in half of the cases it was discontinued entirely. In no case was the rash apparent at the end of two weeks. Edema of the lower extremities occurred in 2 cases. Urinalysis showed no disturbance of kidney function. One case had to be discontinued because of the edema. He thinks that the improvement in these cases may be attributed to the relief of tension and diminution in the severity of the mental conflict, giving an opportunity for the strivings toward reality to dominate and by the stimulation of inhibition thereby strengthen that portion of the

psyche which is striving toward reality. He feels that bromid frequently brings about a return of interest in the field of former activity, the patients become more readily accessible, are more easily influenced and the level of consciousness is raised. He summarizes the results as follows: Of 69 cases of dementia precox treated, 51 showed varying degrees of improvement, 18 were unimproved, 3 manic depressive cases all showed a varying degree of improvement, 6 of the functional psychoses showed improvement in 4 while 2 were unimproved. In 8 organic cases 5 showed varying degrees of improvement and 3 were unimproved. "The results in dementia precox were found to be more lasting, many cases having risen from the vegetative level to a level in which they were taking considerable interest in their surroundings and were usefully employed; some have shown only partial regression, others no regression toward their pretreatment state. In the other forms of functional psychoses treated the percentage of improvement was about equal to that found in the dementia precox group; however, the results were not so lasting." (In commenting on the above would state that in the last 400 admissions to the Colorado Psychopathic Hospital examined consecutively for blood bromid determinations, 19 have shown increased blood bromid, in every one of which mental symptoms were correlated with the bromid intoxication and disappeared on the discontinuance of the drug and its elimination by saline therapy. Among these were some cases of dementia precox, evidently precipitated by the administration of the drug, showing marked improvement on its discontinuance with the patient going into a prolonged residual state requiring institutional care. Because of these facts the abstractor would advise against experimental use of bromids in large doses without carefully controlled determinations on the blood serum of the patient. Our own experiences would contraindicate the extensive or intensive use of bromids in the treatment of mental and nervous diseases.)

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**The Treatment of Schizophrenia.**—HINSIE (*The Psychiatric Quarterly*, 1929, 3, 5) presents a rather extended study of present-day methods of treating schizophrenic patients. In discussing psychotherapy he gives a great deal of space to psychoanalytic treatment and mentions only briefly such general methods as reëducation, training, activity régimes, encouragement and suggestion. He believes from the observations which he collected that patients with schizophrenia form a wide and varied group and that a single therapeutic approach is ill-advised. The status of biological processes in the treatment he considers to be as yet uncertain except in those cases where there is a definite malfunction or deficiency of one of the endocrine organs. He presents considerable evidence that prolonged narcosis has proved of value from the pharmacotherapeutic standpoint but believes that so far no adequate safe method for inducing prolonged sleep has been advanced. Fever therapy he considers has not yet been proven of any definite value. So also serotherapy, the treatment of focal infections, physiotherapy and various surgical procedures, he believes to be of value only in the presence of specific indication for such intervention. Occupational therapy he considers to be of value as an adjunct to other forms of treatment. In summary he states: "It appears from the

works of others that the broad psychobiologic approach has rendered better service in the general management of schizophrenic problems than have other forms of treatment. Psychotherapeutic investigations have likewise been reported as yielding favorable results under the circumstances particular to the nature of the drug employed. A third plan comprises a combination of the first two methods. In some cases combined treatment is a method of choice, either the psychical or the pharmaceutic procedures being emphasized, depending on the special circumstances surrounding the case. Ordinarily drug therapy appears to be useful as a means by which the patient may be rendered accessible to psychotherapy. Occupational therapy occupies a somewhat similar position, in that it affords the patient an opportunity to express his needs and his interests and by the expression the way is open for more profound investigation and treatment of the psychological issues peculiar to the case at hand."

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## PATHOLOGY AND BACTERIOLOGY

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**Metaplasia of Basal Cells in the Ducts of the Pancreas.**—The presence of plaques of squamous epithelium in the ducts of the pancreas have been commented upon by many authors. These have usually been described in association with other lesions of the ducts, obstruction, cyst formation and stone. BALO and BALLON (*Arch. Path.*, 1929, 7, 27) observed a metaplasia of basal cells in the pancreatic ducts in over 8 per cent of 160 pancreases examined. These islands of metaplasia occurred in both the large and small ducts, and varied greatly in the extent of involvement of these tubules. The authors believe that these lesions which appear as projecting masses account for dilatation and cyst formation in the distal portions of these tracts. Other pancreatic changes may also be referable to their presence. A considerable proportion of the cases were accompanied by jaundice. They state that it is possible that factors similar to a deficiency of vitamin A may play a rôle in the proliferation of the basal cells of the ducts of the pancreas.

**Siderosis of the Globus Pallidus: Its Relation to Bilateral Necrosis.**—HADFIELD (*J. Path. and Bacteriol.*, 1929, 32, 135) studied a series of 65 brains to determine the variation in the localization of iron deposits. He found that siderosis limited with anatomic precision to the globus pallidus is the expression of a slow evolutionary atrophy affecting the nuclei in at least 60 per cent of individuals over the age of thirty years.

Its presence cannot be taken as indicating the presence of any disease process, although this deposit predisposes to acute bilateral destruction of these nuclei. The siderosis is of endogenous origin, arising, he believes, from the nerve cells and neuroglia and accumulating in visible and stainable form in the perivascular spaces. The iron deposit at times, bears a relation to the deposition of calcium, and the presence of sclerotic arteries.

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**Diffuse Obliterating Endarteritis of Unknown Etiology.**—PERLA and SELIGMAN (*Arch. Path.*, 1929, 7, 55) report a case of diffuse obliterating endarteritis in a woman, aged forty-seven years, who for a period of one year prior to death showed manifestations of cerebral sclerosis. At autopsy an extensive endarteritis was found to involve the coronary arteries of the heart, cerebral, renal, splenic, thyroid, pulmonary and peripheral vessels. The inferior vena cava was also sclerosed and thrombosed. The vascular sclerosis were mainly composed of nodular thickenings of the intima encroaching upon the lumina of the vessels. No etiologic factor could be determined for the condition. They state that they were able to find only one other case of similar nature.

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**The Influence of Fatigue on the Exchange of Water in the Body.**—Recent research has shown that the changes in the concentration of the blood after fatigue are not so simple as formerly represented. Tests were made on the blood by KAULBERSZ (*J. de physiol. et path. gén.*, 1928, 26, 616) after varying periods of fatigue, caused by walking or climbing. It was found that the loss of water by perspiration and evaporation did not necessarily cause a greater concentration of the blood, but was accompanied by a dilution, by a protein containing liquid, arising after muscular activity. The heat of the body was particularly noted, and the amount of water drunk during the fatigue, taken into account. The latter was found to cause no appreciable dilution. First short tests, of an hour and less, showed a gradual increase in the concentration of the blood, following a rapid dilution during the first few minutes of walking, with a constant rise in temperature from the first. In longer tests of several hours, the concentration diminished after the first hour, and the blood became more and more diluted by the protein-containing liquid, while the temperature of the body decreased gradually. Thus the tests showed that the changes of the water in the blood depended on the temperature of the body, and fatigue in physical work produced a concentration and dilution of the blood according to the rise and fall of the heat of the body.

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**The Progressive Anemia following a Single Intramarrow Injection of Bacillus Welchii Toxins.**—TORREY and KAHN (*Am. J. Path.*, 1929, 5, 117) have been able to demonstrate that the single inoculation of 0.5 cc. of a Bacillus welchii toxin (only slightly hemolytic *in vitro* but of a potency sufficient to cause death in twenty-four hours when injected into the breast muscles of a pigeon) into the tibial marrow of rabbits and a monkey was followed by a widespread degenerative process of the bone marrows. The commencement of these changes was noted on the side of the body opposite the site of inoculation within eighteen hours. After



twelve days the process was well advanced as shown by the marked mucous degeneration of the fat cells, great diminution in other normal marrow and blood-forming cells and a marked increase in polymorphonuclear leukocytes. In rabbits which had died eleven or more weeks after the inoculation the marrows were found to be in an advanced stage of degeneration with fat cells replaced by a granular material and an extreme atrophy of cellular elements. Nearly all the animals showed a rather more pronounced degeneration in marrows far removed, than in that into which the toxin was injected. The concomitant clinical picture and hematology in these animals was evidenced by a chronic, persistent, and often fatal anemia characterized by a low hemoglobin content of the blood, low erythrocyte count and a color index generally above 1. Anisocytosis and at times poikilocytosis was pronounced. An intravenous injection of like or larger amounts of toxin caused a similar anemia but only a transitory marrow injury which was followed by protection from the effects of later and larger amounts of the toxin.

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## HYGIENE AND PUBLIC HEALTH

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**A Special Study of the Vision of School Children.**—KEMPF, JARMAN and COLLINS (*Pub. Health Repts.*, 1928, 43, 1713) review the anatomy of the eye, the physiology of vision, the principles of optics and give a detailed study of the eyes of 1860 children in the Washington public schools. Special points in the general discussion are the rapid development of myopia between the seventh and twelfth year and the importance of examinations by specialists. The following are the important features brought out by this survey: (1) The simple Snellen test reveals but a small percentage of the actual number of refractive errors in children. (2) The myopic eye is nearly always discovered with the use of the simple Snellen test. (3) The hyperopic eye is rarely found with the simple Snellen test, and then only the very severe types are revealed. (4) The astigmatic eye may be found with the simple Snellen test. Of course the simple Snellen test does not reveal the type of visual defect; it shows only that certain eyes can read only certain letters at a specified distance. (5) The frequency of myopia tends to increase between the seventh and twelfth years. This is very important, as myopia may develop rapidly. For this reason all school children

should have the simple Snellen test twice a year. (6) Of the 66 per cent of eyes which read 20/20 or better and appeared normal, 32 per cent read 20/50 or worse when a cycloplegic was used, thus indicating that many eyes work under a handicap. Nearly one-fifth of all the children tested 20/100 or worse after the cycloplegic. (7) The hyperopic eye tends to improve with advancing school age. (8) The myopic eye tends to grow worse with advancing school age. (9) The results emphasize the necessity for regular annual examination of eyes which are known to be defective.

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**A Series of Typhoid Fever Cases Infected per Rectum.**—HERVEY (*Am. J. Pub. Health*, 1929, 19, 166) reports 13 cases of typhoid fever occurring in a hospital of 118 beds, all among a group of 20 surgical patients, to each of whom a rectal drip had been administered. Gross pollution of drip apparatus occurred regularly when in use. After use the containers were rinsed but not sterilized. Other routes of infection have been excluded beyond reasonable doubt. Case I developed typhoid on the fourteenth day after admission to the hospital and it is not unreasonable to postulate that he was infected before admission. No other sources of infection were found on laboratory examinations of the excreta and blood of other patients, attendants, etc. In the instance of Case II, an apparatus known to have been taken directly from Case V was used and typhoid developed eight days later. A hypothetical sequence in the exchange of apparatus, compatible with known facts, has been shown, which would account for the entire epidemic.

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**On the Significance of Spleens Palpable on Deep Inspiration in the Measurement of Malaria.**—MAXCY, BARBER and KOMP (*Pub. Health Repts.*, 1927, 42, 3010) summarize their studies as follows: In the United States where malaria is lightly endemic and there is a widespread use of quinin, the spleen and blood rates are low in comparison with tropical countries. If the technique of spleen examination be made more delicate, there are included with the definitely pathologic spleens a large number of normal spleens which are just palpable on inspiration, and spleens slightly enlarged or rendered more palpable by a recent infection, such as, for instance, measles. The inclusion of this class of spleens tends to obscure comparisons which may be made of the malaria spleen rate in different population groups. It is the spleens which are easily palpable at the costal margin or below, on normal respiration, which are of significance in the measurement of malaria. Field workers should control their spleen technique by observations made in a nonmalarious locality, and show the spleen composition or classification in all examinations made in malarious localities.

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**The Incubation Period of Poliomyelitis.**—AYCOCK and LUTHER (*J. Prev. Med.*, 1929, 3, 103) collected data bearing on the incubation period of poliomyelitis from the following sources: milk-borne outbreaks; cases following tonsillectomy; isolated groups of cases in the same locality where contact could not be traced; cases where a single known contact occurred; certain instances of multiple cases in families

where the individuals had separated before onset of the disease; and an analysis of all cases observed in 1928 in Massachusetts, with known contact, in which an interval of separation had occurred prior to onset. They found that in all cases where the time of exposure can be set within narrow limits the apparent incubation falls within a period of from six to twenty days. In all cases where the last exposure occurred less than six days preceding onset of the secondary case, the duration of exposure is such that the incubation period could likewise have fallen within these limits. In none of the observations reported in this paper was the incubation period necessarily shorter than six days. In some of these observations there is evidence that the infectious period of the disease may extend from the fourteenth day preceding the onset of symptoms to at least the fifth day of the disease. The incubation period observed in the experimental disease in monkeys following inoculation of fully active virus was most often six or seven days, but varied from four to fifteen days. Longer incubation periods were observed following inoculation of modified virus.

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**"Food Poisoning" Produced in Monkeys by Feeding Live Salmonella Cultures.**—DACK, JORDAN and WOOD (*J. Prev. Med.*, 1929, 3, 153) state that the majority of recent experimenters have met with signal failure in attempts to produce characteristic gastrointestinal symptoms by feeding animals with heat-killed Salmonella strains. Rhesus monkeys and young animals of various kinds have remained entirely unaffected after being fed large quantities of freshly isolated bacterial strains of known food poisoning history. No case of illness developed in 24 human volunteers who were given large amounts of heat-killed cultures and filtrates of *Salmonella ærtrycke* and *Salmonella enteritidis*. In view of these negative results, the authors considered it possible that the symptoms of "food poisoning" might be due to substances in the living bacilli. Accordingly, eleven rhesus monkeys were fed with living instead of heat-killed cultures of two strains of the salmonella group. The animals manifested definite and characteristic signs of "food poisoning:" watery diarrhea and general malaise with, in some cases, loss of appetite. Recovery was prompt and apparently complete; the specific bacilli were not found in the blood stream. A second attack could be produced in the same animal after a short interval. Monkeys fed with equivalent heat-killed portions of the same suspension showed no symptoms. Likewise, feeding with living cells of *Proteus* and *Bacillus coli* failed to produce any noticeable effect.

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**Infection of Laboratory Worker with Bacillus Influenzæ.**—WALKER (*J. Infec. Dis.*, 1928, 43, 300) describes the course of a laboratory infection with Pfeiffer's bacillus. The symptoms consists of rhinitis, conjunctivitis and bronchitis. There was no fever. Organisms serologically identical with the laboratory strain were isolated from the nose, conjunctivæ and sputum. The disease would ordinarily be classified as a severe cold, although the diagnosis of sporadic influenza cannot be entirely eliminated. The infection demonstrates anew that some strains of the organism have an extraordinary avidity for attacking respiratory mucous membrane as the primary cause of the disease.

## PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 20, 1929

**A Comparison of the Composition of Pancreatic Juice and of Blood Serum under Experimental Conditions.** — ERIC G. BALL and D. WRIGHT WILSON (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania, Philadelphia). A study has been made of the relations that exist between the concentrations of the inorganic constituents of pancreatic juice and blood serum of the same animal.

Dogs were given amytal intraperitoneally and the major pancreatic duct cannulated. Secretin as prepared by the method of Cowgill and Mendel was injected intravenously. A flow of clear colorless juice was produced varying in amounts from 0.3 cc. to 1.5 cc. per minute, depending on the size of the dog. The juice was collected under oil in a graduated centrifuge tube to permit the measurement of the rate of flow which determines the concentration of some of the constituents. Micro methods of analysis were used throughout and in some cases checked against macro procedures.

Calcium, magnesium and phosphate were found in pancreatic juice in concentrations  $\frac{1}{3}$  to  $\frac{1}{4}$  of that in blood serum. The intravenous injection of salts yielding these ions in amounts sufficient to treble the normal serum values did not significantly alter this ratio. This suggests a low permeability for these ions. Sodium concentrations in juice were found to be somewhat higher than in serum, when calculations were made on the volume basis. However, the sodium concentrations calculated per kilogram of water were about the same in the two fluids. Potassium concentrations in the juice and serum were about identical. Injections into the blood stream of sodium chlorid, and potassium chlorid resulted in a parallel rise in the concentrations of these ions in serum and juice. Chlorid and bicarbonate concentrations in juice were found to vary inversely and to vary usually with the rate of secretion; the sum of the two ions being constant and similar to their sum in serum. Juices secreted rapidly had a bicarbonate content six times, and a chlorid content  $\frac{1}{3}$ , that of serum, while slowly secreted juices contained these ions in concentrations more nearly equal to those of serum. Assuming a constant carbon dioxid tension such results indicate that a juice rapidly secreted is more alkaline than one slowly secreted. Freezing point determinations show that the juice and serum have the same osmotic pressures. A comparison of the sum of the acid and base inorganic radicals in juice showed the base to be in excess by about 10 milli-equivalents per liter. This excess of base cannot be bound by the small amount of protein in the juice if the combining capacity of the protein is similar to that of serum protein. It is possible that organic acid radicals are also present to bind part of this base.

**Extra Ocular Reflexes.**—G. P. MCCOUCH and F. H. ADLER (from Department of Physiology, University of Pennsylvania). Photographic records were obtained from the extraocular muscles in decerebrate cats. *Nystagmus*: Though the onset of contraction is synchronous with the onset of relaxation of the antagonistic muscle, relaxation is usually more abrupt, yielding a tension curve concave upward in contrast to the almost linear rise of tension in the opposing muscle. Tensions are low, not exceeding 8 grams. Reflex co-contraction on a background of nystagmus does not alter the reciprocal relation of an immediately succeeding quick component. This result supports de Kleins' view that the quick component is not initiated by proprioceptors in the extraocular muscles.

*Winking*: Associated with the wink from stimulation of the conjunctiva there is a retraction of the eyeball mediated by co-contraction of the retractor bulbi and all of the recti muscles, which may attain a tension of 40 grams in the external rectus. The curve of contraction is S-shaped when isometrically recorded, concave upward to a peak when shortening is permitted. It terminates within 70 to 100  $\sigma$  in an angle almost as sharp, and a curve of relaxation almost as abrupt, as occur in a neuromyal tetanus. Such a pattern suggests rapid recruitment followed by almost complete synchronous inhibition.

**The Comparative Molecular Concentrations of Glomerular Fluid and Plasma in Frog and Necturus.**—A. M. WALKER (from the Laboratory of Pharmacology of the University of Pennsylvania). Specimens of glomerular fluid and plasma were obtained from 34 frogs and 5 necturi, and the molecular concentration of the two fluids compared, one against the other. The capillary method of Barger, recently employed by White in a similar investigation on necturi, was employed. In 29 instances the glomerular fluid proved to be isotonic with plasma; and in only 3 of the remaining 10 instances did the glomerular fluid differ from the plasma in molecular concentration by more than 10 per cent. These results are in agreement with similar experiments on dye content and electrical conductivity recently performed in this laboratory; and are taken as strong evidence that glomerular fluid is formed by the simple physical process of filtration.

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ORIGINAL ARTICLES.

THE OUTPUT OF THE HEART IN THYROTOXICOSIS, WITH THE  
REPORT OF A CASE OF THYROTOXICOSIS COMBINED  
WITH PRIMARY PERNICIOUS ANEMIA.\*

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THE combination of thyrotoxicosis and primary pernicious anemia is extremely rare. Only 3 cases have been found in the literature. One was reported by Neusser<sup>19</sup> in 1899, 1 by Hansen<sup>12</sup> in 1922 and the third case was mentioned by Giffin and Bowler<sup>11</sup> in 1923. Neusser's case came to autopsy and was found to have a condition of the liver "similar to acute yellow atrophy." Hansen's case developed acutely after repeated Roentgen ray treatment over the thyroid gland. Youmans<sup>29</sup> has observed that in parts of the country where both diseases occur frequently their combination is not seen.

A moderate degree of anemia was for long thought to be a usual accompaniment of thyrotoxicosis. Some fifty years ago Wilks<sup>28</sup> pointed out that "there are those who have been content to attribute the whole of the symptoms [of exophthalmic goiter] to anemia," but relatively recently the careful studies of Kocher<sup>14</sup> and Plummer<sup>21</sup>

demonstrated that the pallor frequently observed is not necessarily indicative of reduction in hemoglobin and that significant anemia is, in fact, unusual. Occasionally, it is true, mild secondary anemia is observed to decrease with improvement in thyrotoxicosis.

In hypothyroid states, on the other hand, anemia is the rule. In Kocher's<sup>13</sup> description of cachexia strumipriva he includes the report of a study of the blood of 17 cases. Ten of these had fewer than 3,500,000 erythrocytes per c.mm. MacKenzie<sup>16</sup> has recently emphasized the occurrence of anemia in cases of myxedema. In certain cases the differential diagnosis of myxedema from pernicious anemia may offer some difficulty, and Boothby<sup>5</sup> mentions a case in which he felt sure the two conditions coexisted. Warfield and Greene<sup>27</sup> have made a valuable study of a group of cases of hypothyroidism without myxedema which showed a chlorotic type of anemia.

It is of interest also to note that there has been placed on record by Tyrrell<sup>26</sup> a case of polycythemia vera complicated with hyperthyroidism. This patient has over 9,000,000 erythrocytes per c.mm., and, in addition, struma, tremor, tachycardia and nervousness.

There have been many previous studies on the effect of anemia on the output of the heart and on the effect of thyrotoxicosis. Plesch<sup>20</sup> studied both conditions in 1909, and, in spite of the difficulties of his method, was able to demonstrate increased cardiac output in both. The problem of the circulatory adjustment in anemias has recently been studied by Richards and Strauss,<sup>24</sup> using in general the methods utilized by us in the present study. The effect of thyrotoxicosis on the cardiac output of man has been investigated by Meakins, Davies and Sands,<sup>7</sup> Robinson,<sup>25</sup> Liljestrand and Stenström<sup>15</sup> and Rabinowitch.<sup>23</sup> Blalock and Harrison<sup>3</sup> studied the output of the heart in dogs to which thyroid extract had been administered. No two groups of investigators used the same method, yet all, with the exception of Rabinowitch,<sup>23</sup> agree that the cardiac output is significantly increased. In the case repeatedly studied by Robinson<sup>25</sup> the cardiac output was actually increased to a greater degree than the oxygen consumption of the body. This is important because it means that the work of the heart was increased out of proportion to the increase in the metabolic rate.

This study, which was initiated because of the combination of two conditions, each demanding an increase in cardiac output, was continued after the relief of anemia in an attempt to study the relation between changes in the degree of thyrotoxicosis and cardiac output.

**Case Reports.** CASE I.—F. S., a white farmer, was first seen by one of us in January, 1926, when he entered the Vanderbilt University Hospital. From his own recollection and the previous hospital records the following history was obtained:

In 1915, when twenty-three years of age, he noticed that he tired with increasing ease on exertion. He felt weak and nervous, his eyes became prominent and his neck increased in size. At this time he was told by a physician that he had a goiter and operation was advised. He decided against operation, and his condition until 1918 was variable; sometimes he felt quite well and was able to perform his work without difficulty; at other times he relapsed into the condition of restlessness and fatigability.

In 1918 he again consulted his physician and consented to submit to an operation. He was given Lugol's solution for some days and then a partial thyroidectomy was performed. Following this procedure he felt almost well for about two years, but in 1920 he had again the old symptoms of nervousness and weakness. These symptoms persisted intermittently until 1924. At this time the nervousness and weakness were accompanied by sensations of numbness and tingling of the extremities with shortness of breath on exertion and some swelling of the feet and ankles. With this combination of symptoms he entered the Vanderbilt University Hospital. There the basal metabolic rate was found to be +57. The red blood cells numbered 4,730,000 and the hemoglobin was 90 per cent. After two weeks of rest and the administration of Lugol's solution he was discharged "slightly improved." The diagnosis recorded was "toxic goiter." During 1924 and 1925 he received several Roentgen ray treatments over the thyroid gland without manifest improvement.

When he was admitted to the Vanderbilt University Hospital in January, 1926, he was obviously seriously ill. He presented marked exophthalmos, an enlarged thyroid gland, tachycardia and tremor. The basal metabolic rate was +47. He had at this time a palpable spleen, brownish pigmentation over the front of the neck, a normal tongue and achlorhydria. The red blood cells were 1,200,000, the leukocytes 3200 and the hemoglobin 24 per cent (Sahli). The stained smear showed some slight variation in size and shape and no young forms. There was no evidence of involvement of the spinal cord.

Four transfusions resulted in a rise in erythrocytes to 3,000,000. In April, three months after admission, after preparation with iodine, thyroidectomy was attempted. The procedure had to be abandoned before any gland tissue was removed because of uncontrollable oozing from the gland. Operation was rendered difficult also by dense adhesions about the gland, possibly due to Roentgen ray therapy. Treatment after this consisted of rest in bed, iron and arsenic. On May 14 he was discharged improved, with the basal metabolic rate +33. The red blood cells on the day of discharge numbered 3,190,000, the leukocytes 3800 and the percentage of hemoglobin was 52. He was advised to rest for a period of six months. After this period he began light manual labor in a restaurant and was able to work until November, 1927. He was then forced to abandon work because of the return of weakness, nervousness, shortness of breath and palpitation.

On December 14, 1927 he sought admission to this hospital for the third time. Examination showed him to be again seriously ill. He was pale, emaciated and dyspneic, and showed a fine tremor and striking exophthalmos. The tongue was smooth and atrophied. The heart rate was 150, the rhythm regular. The neck veins were distended, there were râles in the bases of both lungs and pitting edema of the ankles. The vital capacity was 39 per cent of the calculated normal.

The blood contained 1,000,000 erythrocytes and 1800 leukocytes per c.mm. The hemoglobin was 20 per cent. The stained smear showed deeply-staining cells, irregular in size and shape and with a tendency to macrocytosis, but no nucleated cells were seen. The icteric index was 10. The basal metabolic rate the day after admission was +90.



The patient was given a transfusion of 500 cc. of blood on the third day of his admission and the administration of digitalis was begun. Definite improvement followed transfusion. At the same time he began to receive 200 gm. of raw liver daily.

His course from this point can best be followed by inspection of Figs. 1 and 2. The response to the liver diet was immediate and striking, and was similar to that described by Minot<sup>18</sup> in uncomplicated cases of pernicious anemia. The reticulocytes rose to 17 per cent and then fell to a level slightly above normal. The red cells increased in number steadily and rose more rapidly than did the hemoglobin percentage. During this period the symptoms of thyrotoxicosis diminished to a marked degree and then gradually grew worse again. Accordingly some two months after admission, when the red blood cells approached 5,000,000 per c.mm., the patient was given 0.6 cc. of Lugol's solution three times daily. Three weeks later the administration of digitalis was discontinued. When the "iodin remission" (Fig. 2) had taken place the dose of Lugol's solution was reduced so that he was receiving 3 mg. of iodine daily, following the suggestion of Marine.<sup>17</sup> This ration was further reduced to 1 mg. daily two weeks later. Periodically, he received also ergotamin tartrate which according to the view of Adlersberg and Porges<sup>1</sup> acts as an inhibitor of the sympathetic system, and hence as an antagonist to thyroxin. This combination of minute doses of iodine with ergotamin was first suggested by Youmans.<sup>29</sup>

The patient left the hospital ninety days after admission, but his progress has been followed regularly in the out-patient department and he has three times entered the wards (admissions 4, 5 and 6) for short periods of observation. When last seen, on June 22, 1928, he was obviously in good general condition. He was working as a watchman. His blood contained 5,000,000 red cells per c.mm. and 90 per cent of the expected hemoglobin. He weighed 66 kg., and his basal metabolic rate was +13.

The combination of severe diminution in the oxygen-carrying power of the blood with a large increase in the oxygen consumption of the body offered an opportunity to study the response of the circulation to an unusual load. At the time of his third admission, when this part of the study was begun, he was suffering from moderate congestive heart failure. This rendered impracticable the application of the more accurate methods for measuring the output of the heart per minute, but an approximate estimate was made by the procedure described by Rabinowitch.<sup>22</sup> The first point on the chart of cardiac output was obtained by this method.

When as a result of the liver diet the patient's hemoglobin concentration approached a normal figure, and when the evidences of congestive heart failure had disappeared the study of the cardiac output was resumed. Later determinations were made by use of the method of Field, Bock, Gildea and Lathrop.<sup>8</sup>

**Results.** The results of these studies are shown in Figs. 1 and 2 and in Table I. The figures concerning the changes in the blood require no further comment. When those concerned with metabolism and the circulation are studied, however, certain observations may be made.

When the metabolic rate was highest (+90) and the hemoglobin lowest (20 per cent) the cardiac output was approximately 20 liters per minute, an amount ordinarily associated only with severe and short-lasting muscular exertion.

Thirty-eight days later the metabolic rate was only +34 and the output of the heart was 10.5 liters per minute, at a time when the

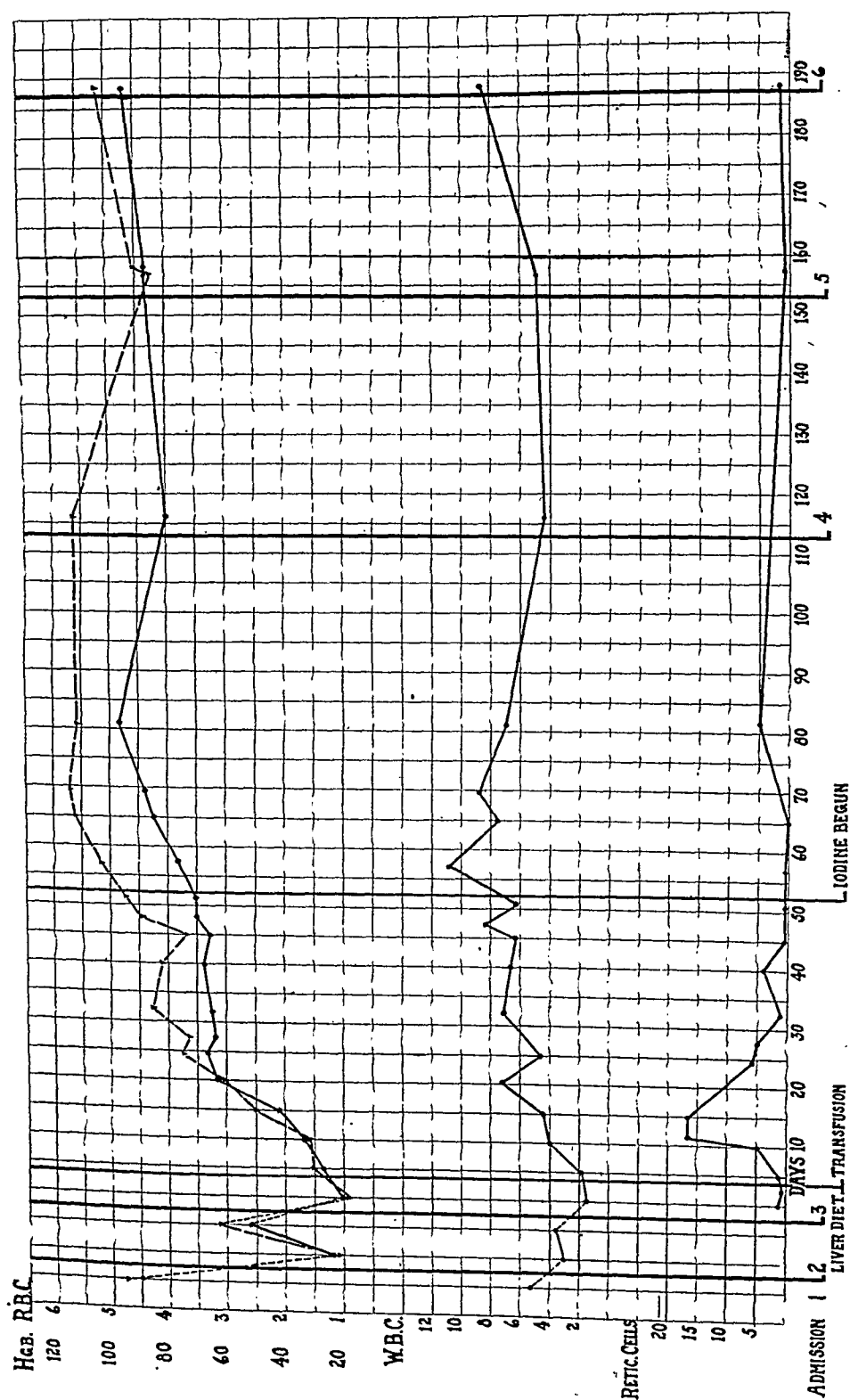


FIG. 1.—The influence of the liver diet on the composition of the blood of Subject F. S.

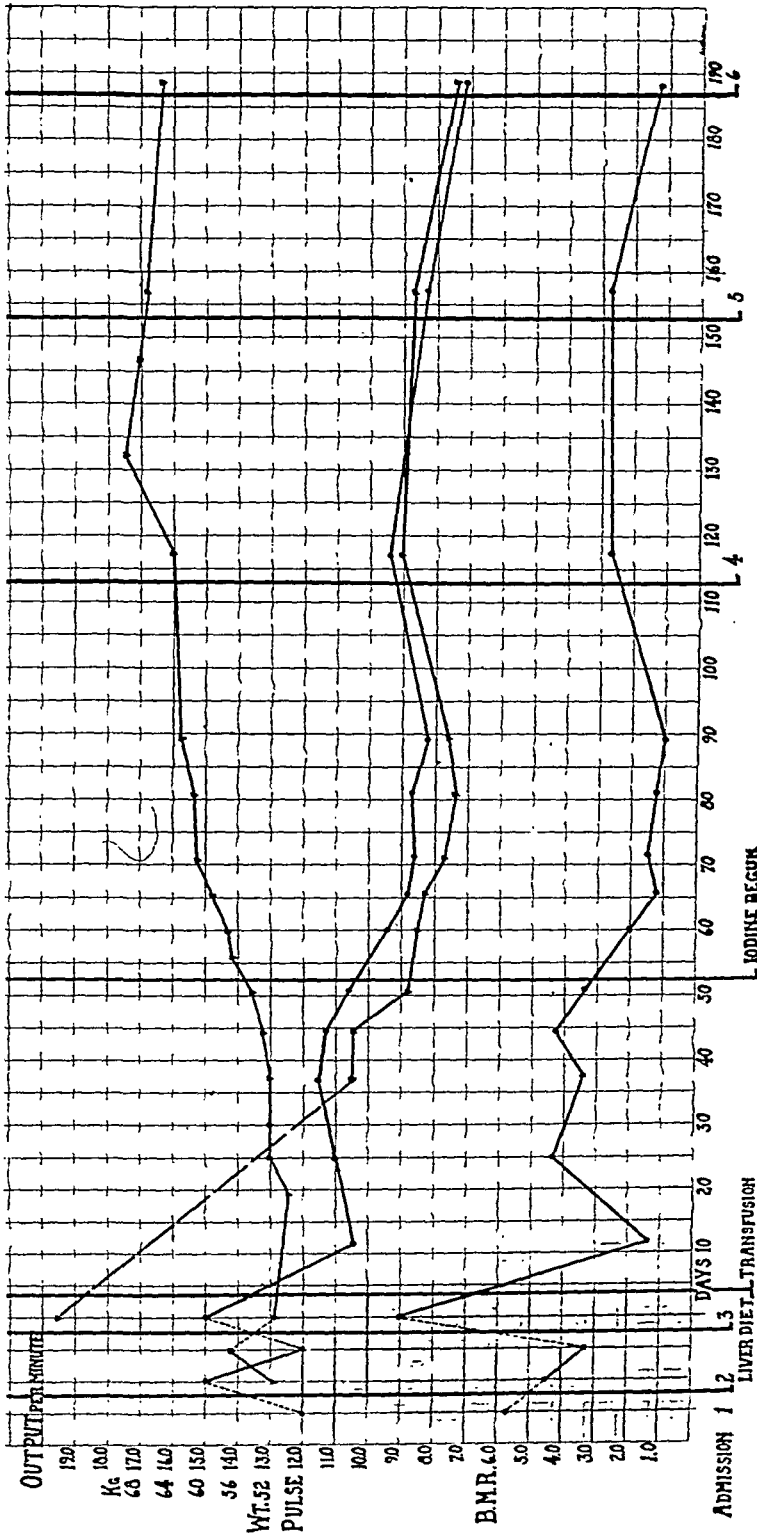


FIG. 2.—Variations in the weight, basal metabolic rate, pulse rate and cardiac output of Subject F. S.

hemoglobin was above the level below which Blalock and Harrison<sup>2</sup> showed that the cardiac output was increased by anemia.

TABLE I.—THE CARDIAC OUTPUT OF SUBJECT F. S. WITH RELATED DATA.

Date.	Erythrocytes, per c.mm. in millions.	Hemoglobin (Sahli), per cent.	Weight, kilo.	Respiratory quotient.	Pulse rate.	Basal metabolic rate, per cent.	Carbon dioxide per min., cc.	Art.-ven. difference, carbon dioxide, vol. per cent.	Cardiac output per beat, cc.	Cardiac output per min., cc.	Cardiac output per 100 cc. oxygen, cc.
1927.											
Dec. 16	1.01	20	51	0.81	150	+90	325	1.67*	130	19,500	4850
1928.											
Jan. 23	4.10	67	52	0.80	116	+34	244	2.32	91	10,500	3450
Jan. 29	3.70	66	53	0.80	114	+42	257	2.44	92	10,500	3250
Feb. 6	4.75	70	54	0.76	108	+33	214	2.39	83	9,000	3200
Feb. 9†											
Feb. 15	5.23	76	58	0.81	95	+20	224	2.60	91	8,600	2800
Feb. 21	5.62	84	60	0.84	89	+12	223	2.66	94	8,400	3150
Feb. 27	5.75	88	61	0.82	86	+15	221	2.77	93	8,000	2950
Mar. 7	5.65	97	62	0.87	86	+13	236	3.17	87	7,500	2750
Mar. 14	...	...	63	0.80	84	+10	217	2.82	92	7,700	2850
April 13	5.67	...	64	0.83	94	+27	258	2.86	96	9,000	2900
May 23	4.58	85	67	0.80	84	+27	249	2.86	104	8,700	2800
June 22	5.20	94	66	0.76	71	+13	216	2.91	104	7,400	2950

\* Calculated from arm vein blood.

† Lugol's solution begun.

Following the administration of iodine, as Lugol's solution, the basal metabolic rate, pulse rate and cardiac output all fell while the body weight increased. Subsequently, the first three factors varied together and, although there was a slight rise in them when the patient began to work, yet all were at their lowest points at the end of the six months' period of observation. It is noteworthy in this case, as in that of Robinson,<sup>25</sup> that increase in the demand of the body for oxygen was met by an increase in the volume of circulation and not by taking from the blood a larger percentage of its oxygen. This occurred in a patient who at the height of his illness had clear signs of congestive heart failure, and is shown by the fact that, as may be seen in Table I, the output of the heart per 100 cc. of oxygen absorbed by the body was greater when the metabolism was higher. The output of the heart obviously increased relatively more than the volume of oxygen absorbed. The cardiac output per 100 cc. oxygen absorbed on December 16, 1927, was 4850 cc., but this increase was, of course, largely due to the severe anemia then present.

As further evidence bearing on this circulatory adjustment to increased oxygen consumption a second case of thyrotoxicosis, similarly studied, is briefly reported.

CASE II.—J. C., a white male, aged forty-eight years, was admitted to the Vanderbilt University Hospital on July 19, 1927, complaining of "nervousness, loss of weight and a rapid heart." He placed the onset of his symptoms at about five years before, when he first noticed that he was nervous and that exertion made him short of breath. These symptoms became progressively worse. He did not sleep well at night, had profuse sweating and was conscious of a rapid heart beat. In spite of a good appetite, he lost 30 pounds in the two years preceding admission. For six months he had noticed that his eyes were more prominent.

With the exception of pneumonia at nine years, his past history was devoid of serious or significant illness.

Examination at the time of admission showed a middle-aged white man with the appearance of having recently lost weight. He was somewhat restless. The face was pale, the lips red and the skin warm and moist.

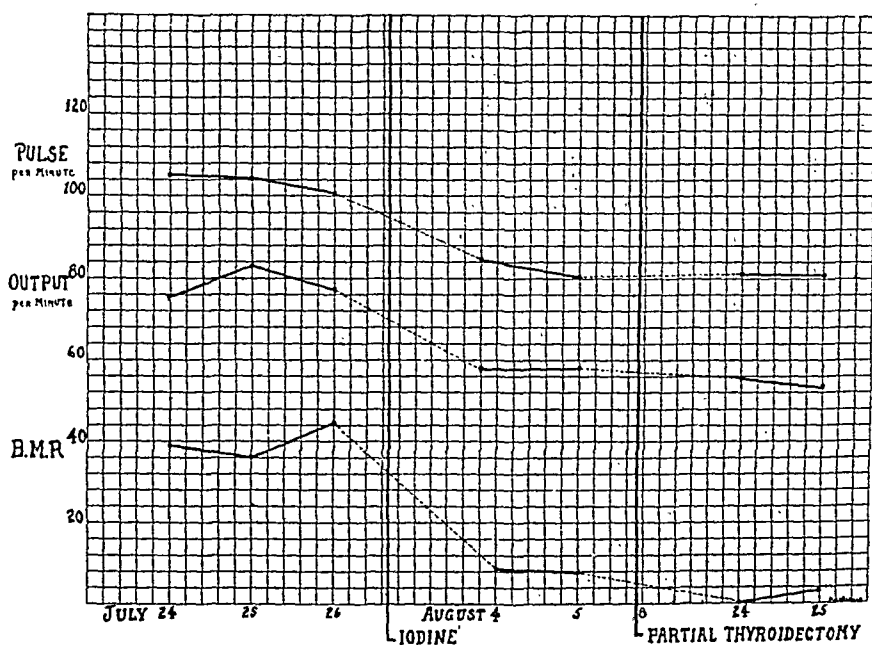


FIG. 3.—Variations in the basal metabolic rate, pulse rate and cardiac output of Subject J. C.

There were moderate exophthalmos, lid lag and poor convergence. The thyroid gland was diffusely enlarged, especially the isthmus and the right lobe. It was firm but not nodular and no bruit was heard. The apex impulse was felt in the fifth interspace 8 cm. from the midline. The blood pressure was 145 mm. Hg. systolic and 75 mm. diastolic.

There was a fine tremor of the fingers and of the muscles of the arm.

The red blood cells numbered 3,700,000, the leukocytes 3200 and the hemoglobin was 70 per cent. The basal metabolic rate at this time was +69.

Following rest in bed the basal metabolism dropped to +37 the fifth day after admission. At this time the study of the cardiac output was begun. A few days later he was given Lugol's solution, 10 drops, three times a day, and after eight days of its administration the pulse rate was 85 per minute and the basal metabolic rate +9. Five days later, on the nineteenth day after admission, partial thyroidectomy was performed.

The postoperative course was uneventful and thirty-six days after admission the basal metabolic rate was normal and the pulse rate 75 per minute.

Observations on the output of the heart were made first after a few days of rest in the hospital, second after a characteristic iodine remission and third after a successful partial lobectomy had been performed. The results are shown in Fig. 3 and Table II.

**Results.** In general, results were obtained which were similar to those from the study of the first case. The pulse rate, metabolic rate and cardiac output varied together and the final figures for the output of the heart are similar to those observed in many normal people. In this patient also the cardiac output was increased to meet the increased oxygen demand without decreasing the oxygen content of the mixed venous blood.

TABLE II.—THE CARDIAC OUTPUT OF SUBJECT J. C. WITH RELATED DATA.

	Resp. quotient.	Pulse.	Basal metab- olic rate.	Carbon dioxid per min., cc.	Art-ven. differ- ence.	Cardiac output per beat, cc.	Cardiac output per min., cc.	Cardiac output per 100 cc. oxygen absorbed, cc.
1927.								
July 24	0.87	107	+39	239	3.13	71	7640	2780
July 25	0.96	104	+37	260	3.08	81	8450	3120
July 26	0.81	101	+46	237	3.04	77	7800	2660
July 26*								
Aug. 4	0.81	86	+ 9	178	3.08	68	5800	2640
Aug. 5	0.81	80	+ 8	176	3.04	73	5800	2660
Aug. 8†								
Aug. 24	0.79	82	+ 0	162	2.90	68	5600	2730
Aug. 25	0.75	82	+ 3	158	2.94	66	5400	2560

\* Lugol's solution begun.

† Partial thyroidectomy.

**Discussion.** These results serve to emphasize the magnitude of the extra load imposed upon the heart in cases of thyrotoxicosis with an increased basal metabolic rate. The work of the heart is, as was said earlier, dependent on the volume output of blood, by the pressure against which it is pumped and by the velocity imparted to it. A patient with thyrotoxicosis has not only an elevated cardiac output but usually a somewhat increased mean blood pressure and also, as Blumgart and Gargle<sup>4</sup> have shown, a considerable increase in the velocity of bloodflow. It is, therefore, evident that the heart of such a patient is forced to perform a task in excess of normal demands, especially since the increases in output, pressure and velocity are always present and not, like the strains of muscular exertion, intermittent.

As Goodpasture<sup>9,10</sup> has suggested (on the basis of observations on animals intoxicated by thyroxine), the heart forced to weeks of over-

exertion by the stimulus of thyroid intoxication may be abnormally susceptible to the action of the injurious agents, such as infections. There thus exist in thyrotoxicosis, as in many other conditions preceding cardiac failure, both an increased load on the heart and a source of possible injury to the myocardium.

A second point of interest in these observations, a point supported also by the studies of Robinson<sup>25</sup> and of Liljestrand and Stenström,<sup>15</sup> is the increase of the cardiac output to an amount sufficient to supply the oxygen demands of the body without decreasing the tension of oxygen in the mixed venous blood. In Robinson's case the cardiac output was actually increased relatively more than the metabolic rate, so that the mixed venous blood contained more oxygen when the metabolic rate was high than when it was restored to a normal level by treatment. It is an old observation that the rate of the heart is increased more by a certain degree of elevation of metabolism in thyrotoxicosis than it is by a similar elevation due to exercise. It is probable that under the stimulus of a slight elevation of metabolic rate (as in mild muscular exertion) the cardiac output of a normal person increases approximately as much as the oxygen consumption. The fact, however, that in thyrotoxicosis the circulation may be maintained at this high level until the heart is exhausted suggests that in patients with this disease some stimulus is driving the heart to perform an unnecessary and hurtful amount of work.

As might be expected, the favorable results of the administration of iodine included a diminution in cardiac output which was parallel to the fall in metabolic rate. This fall was similar to that observed after iodine in the "hyperthyroid" dogs studied by Blalock and Harrison.<sup>3</sup>

The question of the effect of digitalis in thyrotoxicosis is not advanced toward solution by these observations. The patient received the drug up to the seventy-second day of his stay in the hospital, when it was discontinued. Following its cessation, the level of cardiac output underwent no demonstrable change. In connection with this observation, it may be recalled that Blalock and Harrison describe two dogs with hyperthyroidism in which the cardiac output fell after digitalis and Burwell, Neighbors and Regen<sup>6</sup> have observed a similar effect in normal men. If digitalis can be shown to diminish the work of the heart in patients with thyrotoxicosis it might serve a useful purpose, unless the increase in cardiac output in these cases is in response to some unrecognized need of the body, such as a need for a high oxygen tension in the tissues.

**Summary.** 1. A case of thyrotoxicosis complicated by pernicious anemia is reported.

2. The increased demand for oxygen combined with the decreased

oxygen-carrying power of the blood was met by a great increase in the cardiac output per minute and hence in the work of the heart.

3. Repeated observation of the cardiac output in this case and in a second case of thyrotoxicosis revealed that the adjustment of the circulation to increased demand for oxygen took place by an increase in cardiac output rather than by an increased utilization of the arterial oxygen.

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## THE RELATIVE EFFICIENCY OF THE CLINICAL AND THE ROENTGENOLOGIC METHODS FOR SINUS DISEASE DIAGNOSIS.

WITH OBSERVATIONS ON THE INCIDENCE OF SINUS DISEASE: BASED  
ON THE FINDINGS IN 200 ASTHMATICS AND 50 SO-CALLED  
"NORMALS."\*

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IN the course of routine examination of asthma patients for paranasal sinus disease, we were struck by the frequent discrepancies between the reports of findings by the rhinologist and the roentgenologist: discrepancies which were at times due to proven error on the part of one or the other of these examiners. It, therefore, occurred to us to subject a considerable series of asthmatics first to a clinical, then to a roentgenologic sinus examination, and finally to an operative investigation of the affected sinuses: we hoped in this way to learn something of the efficiency and limitations of these two methods for the diagnosis of sinus disease. Our findings are set forth in Part I of this paper. In order to estimate correctly the importance of the high incidence of sinus disease in bronchial asthma, it is necessary to take into consideration, among other

\* Co-winner of Casselberry Prize for 1929 awarded by the American Laryngological Association.

things, the incidence of sinus disease in a control group of individuals, not affected at the time of examination by obvious acute or chronic respiratory disease. A search of the literature failed to disclose any data on sinus-disease incidence in so-called "normals." We, therefore, examined clinically and by Roentgen ray a series of 50 such individuals, selected in age groups to correspond to the age distribution of our 200 asthmatics. The findings are included in Part II.

## PART I.

**Material.** Two hundred patients with bronchial asthma as seen in the asthma clinic and the wards of the Hospital of the University of Pennsylvania formed the basis of this study. Ranging in age from four to eighty-one years, they were unselected, except that individuals who had previously been subjected to sinus surgery were excluded. This was done because a sinus that has been operated upon will usually thereafter appear abnormal in the roentgenogram. The clinical examinations were made by the members of the staff of the Department of Otolaryngology, and the Roentgen ray examinations in the Roentgenologic Division of the Hospital.

**The Clinical Examination.** This was made first in every instance. Previous experience had taught us that the clinical examiner might be unduly influenced by the Roentgen ray report: with a previous knowledge of the Roentgen ray findings the otolaryngologist's report tended to agree with the roentgenologist's far more frequently than was otherwise the case. The examiner was told, however, that his findings would be compared with those of a subsequent Roentgen ray examination. If he failed to mention one or another sinus in his report, he was asked to reexamine the patient. In the tabulation of our material, all "suspicious" reports were classified as positive findings, for reasons to be stated later.

If all examinations had been made by a single man of long experience, it is quite probable that the general average of results would have been higher than it proved to be. In a review of numerous reports of otolaryngologic examinations, it soon becomes evident that the examinations of one or two observers are more comprehensive than those of their colleagues, and subsequent surgical investigation usually demonstrates their greater accuracy. The man with the wider experience will emphasize in his report conditions often neglected by the less experienced: points of contact, for instance; the finer shades of transillumination change, or the state of the mucosa of the ethmoid drainage area as seen by the nasopharyngoscope and its bearing on the likelihood of ethmoidal disease. It was interesting to note, however, the greater care and increasing skill displayed by the younger men under the stimulus of anticipated roentgenologic and surgical check-up.

It may be considered pertinent to the subject to state what a

satisfactory nose and throat examination should include. Its essence is thoroughness and completeness. Negative as well as positive findings should be specifically stated. After a survey of the extranasal architecture, both nares should be examined by means of the nasal speculum and head mirror: (a) before cocaineization or the use of ephedrin and (b) after cocaineization and shrinkage of the erectile tissue. There should be a notation of the condition of the septum (deviation, spurs, ridges) of the turbinates (including a notation of points of contact and degrees of contact), of the state of the mucous membrane (pallor, injection, polypoid degeneration, etc.), of the condition of the middle meatus and of the olfactory cleft, of the character and location of secretions, of the presence or absence of anterior synechiæ and obstructions to nasal drainage. The frontal and maxillary sinuses should be studied by transillumination and, when feasible, the antra inspected by the antroscope. Especially to be emphasized is the nasopharyngoscopic examination, with particular attention to the ethmoidal and sphenoidal drainage areas. It cannot be too strongly stated that no examination can be considered adequate without the use of the nasopharyngoscope: it is as essential in nasal examinations as is the cystoscope in the study of the urinary tract.

In forming his opinion of the state of the sinuses, the otolaryngologist has numerous difficulties to encounter. Transillumination is available for examining the frontal and maxillary sinuses. But light transmission may be altered by numerous anatomic variations: variations incident to age and sex; variations in thickness of bone and in size of the sinus; asymmetry, bony septa or the congenital absence of a sinus, and such altered light transmission may create an erroneous impression of the actual condition of frontal or maxillary sinuses. For the rest, the examiner's information must be gathered from intranasal observation: this is often enough limited by such conditions as marked septal deformity or the presence of large polypoid masses. The finding of pus in certain regions, or of degenerative changes in the mucous membrane in these regions, especially as seen with the aid of the nasopharyngoscope, is, of course, most significant: but the overlapping of drainage areas of the different sinuses may again confuse the issue. Pus from both frontal and anterior ethmoidal cells is discharged into the middle meatus. Moreover, the anterior ethmoidal cells also frequently extend forward beneath the floor of the frontal sinus so that involvement of either may give rise to external tenderness in nearly the same position. The ostia of the posterior ethmoidal cells open into the posterior portion of the superior meatus and drain upon the posterior half of the middle turbinate. The sloping of the middle turbinate downward and backward directs the secretion toward the posterior choana, but the secretion also flows over the median border of the middle turbinate through the olfactory fissure, the

space between the turbinate and the septum. Purulent secretion in the olfactory fissure may, therefore, be indicative of posterior ethmoidal suppuration, but is not necessarily so: pus from the sphenoidal sinus may also drain onto the posterior end of the middle turbinate as well as directly into the epipharynx through the posterior choana. Sphenoidal suppuration may at times be recognized by direct observation of the sinus ostium through the nasopharyngoscope, but unfortunately in over 70 per cent of cases the ostium is hidden by the approximation of the middle turbinate to the septum. Finally, the absence of pus in a drainage area does not rule out sinus disease. This is especially true of the low-grade chronic infections and polypoid change. Therefore, in patients in whom the history strongly suggests the possibility of sinus disease, it would be wise to repeat the examination on several occasions before giving a negative report.

**The Roentgenologic Examination.** While this was made after the clinical examination, the roentgenologist was not informed of the clinical findings. His report was, therefore, likewise an entirely independent and unaided one. The terminology used by the roentgenologist in framing his opinion reflects his attempt to interpret, as well as describe, the changes found in the films: "thickened mucous membrane," "polyps in sinus," "hazy," "slight clouding," "some clouding," "dense clouding." In our tabulation of the findings all abnormalities, irrespective of degree, were listed as positive.

The roentgenologist, also, is confronted by certain difficulties. He must consider variations incident to age and sex, asymmetry, bony septa, variations in bone thickness, the congenital absence of a sinus. Sinuses may be so situated that the shadows of adjacent cell groups will overlap. Permanent change in bone or mucosa may have resulted from previous sinus disease or from disease involving the sinus wall from without, as in the case of pathologic dental conditions involving the antrum. Acute disease may be too recent in origin to have produced roentgenographic change.

Roentgenographic technique in sinus examination has been considerably improved in recent years, with a correspondingly greater accuracy in the findings. When only one anteroposterior view and one lateral view were taken there was invariably superposition of sinus shadows with resultant blurring and confusion of outline. This may be avoided in a measure by more numerous exposures and at angles suited to the particular sinus in question. It may be of interest to describe in part the technique employed by, although not original with, the Roentgenologic Division of the University Hospital.

**Roentgenologic Technique.** In order to obtain a satisfactory postero-anterior image of the frontal and ethmoidal sinuses, it is necessary to project the Roentgen rays through the head in this manner: An inclined

plane of 23 degrees is used and the forehead and nose are placed upon the cassette. The tube is placed above the occiput and the Roentgen rays are projected upon the film, the line of the central ray approximately passing through the external occipital protuberance and the glabella. The resulting film shows the frontal and ethmoidal sinuses, and to a slight extent the antra. The petrous ridge extends through the lower third of the orbit. For the examination of the maxillary sinuses the patient's nose and chin are placed on a cassette in a horizontal plane, and Roentgen rays are projected at an angle of 25 degrees, the line of the central ray passing through a point just below the base of the skull and the middle of the maxillary sinuses. This gives a clear visualization of the entire maxillary sinus without any superposition of the bones of the skull, as the base of the skull is projected above the maxillary sinuses on the resulting roentgenogram. For the examination of the sphenoidal sinuses the coronomental position is preferred, the neck being stretched over a cassette which is on an inclined plane of approximately 15 to 25 degrees, the angle depending upon the length of the neck. The tube is above the head of the patient and the Roentgen rays are projected through the anterior portion of the head, keeping in mind the position of the sphenoidal sinuses and arranging the angle of the tube so that these sinuses will not be projected over the bones of the upper and lower jaws. This view also demonstrates the maxillary sinuses very well. In addition, lateral stereoscopic films are made of the head, as in this view one can get an excellent idea of the depth of the sinuses.

**Operative Check.** In order to get an absolute and complete check on the reports of the two methods of examination, every sinus reported abnormal, clinically or by Roentgen ray, should have been investigated by open operation. Unfortunately, we fell far short of this ideal, and for a number of reasons. Open operation on a frontal sinus is rarely performed except in cases of acute empyema. In not a single one of our patients did this occur. It was impossible to get complete coöperation on the part of clinic patients. Many of them flatly refused any operation. Others, after one or two sinuses had been investigated, failed to return for any further operative procedure. Nor would the otolaryngologists go as far in some instances as we wished them to. They were quite willing to open a sinus that was obviously diseased clinically, but we failed at times to convince them of the desirability to investigate a sinus, suspicious on Roentgen ray but clinically negative. Nevertheless, in spite of all these shortcomings, sufficient data were obtained to be of some value in estimating the efficiency of these methods for sinus-disease diagnosis.

**Examination Findings.** A summary of the clinical and roentgenologic examination findings in the 200 asthmatic patients is given in Table I. The figures are in terms of number of patients.

Attention is called to the high percentage (80.5) of asthmatics showing Roentgen ray evidence of sinus abnormality. The figure for positive clinical findings, while lower than that on Roentgen ray study, still reaches an impressively high level: 67 per cent. In fact, only 13.5 per cent of these patients had no evidence of sinus disease by either examination. But of particular importance

is the complete disagreement between clinical and roentgenologic findings in 25 per cent of the patients. Nor is this all the disagreement: of the 61.5 per cent of patients in whom there was "partial or complete" agreement, there were enough instances of only "partial" agreement to increase materially the total number of discrepancies. It was to find some reasons for this high incidence of disagreement that we undertook the present study.

TABLE I.

	Number of patients.	Percentage.
Total asthmatic patients . . . . .	200	
Roentgen ray examination positive . . . . .	161	80.5
Clinical examination positive . . . . .	134	67.0
Clinical and Roentgen ray involvement (partial or complete agreement) . . . . .	123	61.5
Both Roentgen ray and clinical examinations completely negative . . . . .	27	13.5
Complete disagreement . . . . .	50	25.0
Roentgen ray positive; clinical negative . . . . .	40	20.0
Roentgen ray negative; clinical positive . . . . .	10	5.0

In Table II are given the figures of positive findings for individual sinuses or cell groups as reported by the roentgenologist and the clinician. This table bears no reference to the question of agreement or disagreement between the clinical and Roentgen ray reports.

TABLE II.—INDIVIDUAL SINUS INVOLVEMENT AS REPORTED BY:

	(A) Roentgen ray examiner.		(B) Clinical examiner.	
	Number.	Per cent.	Number.	Per cent.
Right frontal . . . . .	83	41.5	47	23.5
Left frontal . . . . .	80	40.0	47	23.5
Right ethmoidal . . . . .	110	55.0	67	33.5
Left ethmoidal . . . . .	94	47.0	67	33.5
Right sphenoidal . . . . .	37	18.5	21	10.5
Left sphenoidal . . . . .	37	18.5	22	11.0
Right maxillary . . . . .	113	56.5	92	46.0
Left maxillary . . . . .	113	56.5	95	45.5

(These figures do not imply agreement between Roentgen ray and clinical findings.)

It will be noted that in both examinations positive findings were most frequent in the antra, next in the ethmoidal, then in the frontal, and least frequent in the sphenoidal sinuses. The number of clinical positives was less in every instance than the corresponding Roentgen ray figure. As might have been anticipated, the clinical figures approached nearest to the roentgenologic findings in the case of the maxillary sinuses, and lagged farthest behind in the case of the sphenoidal sinuses, in accordance with their relative accessibility. It is, however, a bit surprising that positive clinical findings were closer in frequency to the Roentgen ray findings in the case of the ethmoidal than of the frontal sinuses: the intranasal evidence of

ethmoidal disease, indirect though it be, is apparently more definite than the results of frontal transillumination. It is interesting to note that, with the exception of Roentgen ray reports for the ethmoids, there was practically an equal incidence of positive findings for right and left by both methods of examination. (It may be added at this point that a tabulation of septum deviations in these patients showed an equal number to each side.)

In Table III the clinical and Roentgen ray reports are recorded in terms of the number of patients affected. There is again no reference to the question of agreement between clinical and Roentgen ray findings.

TABLE III.—SINUS GROUPS: INVOLVEMENT AS REPORTED BY:

	(A) Roentgen ray examiner.		(B) Clinical examiner.	
	Number.	Per cent.	Number.	Per cent.
Patients with frontal sinus disease . . .	91	45.5	52	26.0
Patients with ethmoidal sinus disease . .	114	57.0	72	36.0
Patients with sphenoidal sinus disease . .	36	18.0	23	11.5
Patients with maxillary sinus disease . . .	132	66.0	105	52.5

(These figures do not imply agreement between Roentgen ray and clinical findings.)

Turning now to the question of agreement or disagreement between the clinical and Roentgen ray reports for each sinus examined, we find the data in Table IV.

TABLE IV.—COMPARISON OF ROENTGEN RAY AND CLINICAL DATA BY INDIVIDUAL SINUS INVOLVEMENT:

		Agreement.				Disagreement.			
		Roentgen ray + Clin. +	Roentgen ray 0 Clin. 0	Total number.	Per cent.	Roentgen ray + Clin. 0	Roentgen ray 0 Clin. +	Total cases.	Per cent.
Frontal	R	36	107	143	71.5	48	9	57	28.5
	L	32	107	139	69.5	47	14	61	30.5
	All	68	214	282	70.5	95	23	118	29.5
Ethmoid	R	53	77	130	65.0	55	15	70	35.0
	L	48	89	137	68.5	44	19	63	31.5
	All	101	166	267	66.7	99	34	133	33.2
Sphenoid	R	13	152	165	82.5	25	10	35	17.5
	L	14	152	166	83.0	24	10	34	17.0
	All	27	304	331	82.7	49	20	69	17.2
Maxillary	R	76	69	145	72.5	39	16	55	27.5
	L	76	71	147	73.5	35	18	53	26.5
	All	152	140	292	73.0	74	34	108	27.0

Here the evidence of disagreement in the reports is most striking. Of 400 ethmoidal groups (200 right plus 200 left) examined, the

reports disagreed in 133 (33.2 per cent). The disagreements in the case of 118 frontal sinuses (29.5 per cent) and 108 antra (27 per cent) were almost as common. Curiously enough, the sphenoidal sinus findings showed the least disagreement, 69 sinuses (17.2 per cent). There were 4 instances of congenital absence of one frontal sinus as shown in the roentgenogram. Of these, 2 were called "opaque" clinically, while 2 were reported as "normal" on transillumination.

**Operative Check.** How far we fell short of a complete operative check may be seen in Table V. Less than half of the patients submitted to any operative procedure, and decidedly less than half of the suspected sinuses were investigated.

TABLE V.—SUSPICIOUS CASES.

Total patients with one or more suspicious sinuses by clinical or Roentgen ray findings . . . . .	173
Total patients coming to operation of one or more sinuses . . . . .	86
Percentage of patients coming to operation . . . . .	49.7

The operative findings together with the previous clinical and roentgenologic examination findings are given in Tables VI and VII.

**Discussion of Operative Findings.** *Frontal Sinuses.* These may be rather briefly dismissed, for none came to operation. The reasons for this have been stated as: (a) operative difficulties, and, (b) the absence of acute empyema in this series of patients. These reasons are perhaps not adequate on more searching analysis. The possible modes of investigation of the frontal sinuses are: (1) Open operation (obviously not applicable in the overwhelming majority of cases). (2) Irrigation through a cannula introduced into the frontonasal duct. The finding of pus in the washings is, of course, indicative of disease, but the failure to obtain pus by no means rules out disease. This will be discussed more in detail when the antra are considered. (3) Lipiodol may be introduced into the sinuses by the expedient of partially exhausting the sinus-contained air by suction and then allowing lipiodol to be sucked from the nose into the sinus, the patient's head being placed vertex-down. A Roentgen ray film will then give information as to the extent of the sinus, condition of its lining, possible abnormal contents, such as polyps. (The ethmoidal and sphenoidal sinuses may also be studied by this method.) Unfortunately, we were unable to examine any of our frontal cases in this way.

It is to be regretted that no check on the frontal examination findings was obtained, for the lack of agreement between the clinical and Roentgen ray reports was particularly great: 29.5 per cent, a discrepancy for which there is no adequate explanation. Since 80 per cent of this error is accounted for by cases in which the Roentgen ray was positive and the clinical examination negative, it may be possible that a greater degree of chronic pathologic change is



TABLE VI.—INDIVIDUAL SINUS OPERATIONS. (+ = POSITIVE; 0 = NEGATIVE.)

	Number cut.	Found diseased.						Found normal.					
		No.	Roentgen ray findings.		Clinical findings.		No.	Roentgen ray findings.		Clinical findings.		No.	
			No. +	No. 0	No. +	No. 0		No. +	No. 0	No. +	No. 0		
Frontal . . . . .	0	35	32	3	26	9	1	1	0	0	0	1	
Ethmoid . . . . .	36 34 70	33 68	28 60	5 8	25 51	8 17	1 2	1 2	0 0	0 0	0 0	1 2	
Sphenoid . . . . .	10 10 20	8 7 15	6 7 13	2 0 2	5 5 10	3 2 5	2 3 5	0 0 0	2 3 5	0 1 1	0 2 4	2 2 4	
Maxillary . . . . .	56 54 110	28 28 56	27 26 53	1 2 3	23 23 46	5 5 10	28 26 54	25 24 49	3 2 5	19 19 38	9 7 16		

TABLE VII.—TABLE OF PERCENTAGE OF ERROR OF ROENTGEN RAY AND CLINICAL METHODS OF SINUS EXAMINATION, BASED ON OPERATIVE FINDINGS (TABLE V).

	Side.	Total cases.	Roentgen ray correct.	Roentgen ray wrong.	Roentgen ray error (%).	Clinical correct.	Clinical wrong.	Clinical error (%).
Ethmoid . . . . .	R	36	32	4 { 3 Diseased 1 Normal	= 8.3 = 2.8 11.1	27	9 (All diseased)	25.0
	L	34	28	6 { 5 Diseased 1 Normal	= 14.7 = 2.9 17.6	26	8 (All diseased)	23.5
	R + L	70	60	10 { 8 Diseased 2 Normal	= 11.4 = 2.9 14.3	53	17 (All diseased)	24.3
Sphenoid . . . . .	R	10	8	2 (2 Diseased)	= 20.0	7	3 (All diseased)	30.0
	L	10	10	0	= 0	7	3 { 2 Diseased 1 Normal	= 20.0 = 10.0 30.0
	R + L	20	18	2 (2 Diseased)	= 10.0	14	6 { 5 Diseased 1 Normal	= 25.0 = 5.0 30.0
Maxillary . . . . .	R	56	30	27 { 1 Diseased 26 Normal	= 1.8 = 46.4 48.2	32	24 { 5 Diseased 19 Normal	= 8.9 = 33.9 42.8
	L	54	28	26 { 2 Diseased 24 Normal	= 3.7 = 44.4 48.1	30	24 { 5 Diseased 19 Normal	= 9.2 = 35.2 44.4
	R + L	110	57	53 { 3 Diseased 50 Normal	= 2.6 = 45.6 48.2	62	48 { 10 Diseased 38 Normal	= 9.1 = 34.5 43.6

necessary to impair transillumination than to be evident on the Roentgen ray film. If this be true, then transillumination must be considered less accurate than Roentgen ray examination. But there is no adequate direct proof, as far as we know, that the roentgenologist's conclusions are correct.

*Ethmoidal Sinuses.* In the first place, the operative determination of the "diseased" or the "normal" state of the ethmoidal sinuses rests on fairly good evidence: the actual finding of pus, grossly abnormal secretion or the presence of polyps; the demonstration of roughened bone by probing is significant. The chief criticism that might be offered is that smears were not examined routinely for pus and bacteria.

The Roentgen ray error in this group was decidedly less than that of clinical examination. The roentgenologist failed to recognize 8 of 68 diseased ethmoidal groups. Four of these 8 were apparently cases of acute infection and perhaps of recent standing:

**Case Reports.** CASE D6.—Right and left ethmoidal groups were reported negative on Roentgen ray but positive on clinical examination. Frank pus was found in both ethmoidal sinuses at operation.

CASE S18.—Right and left ethmoidal groups were reported negative on Roentgen ray but positive on clinical examination. Frank pus was found in both ethmoidal groups at operation. There was additional sinus disease present.

Polyps were overlooked by the roentgenologist in three instances:

CASE C7.—Right and left ethmoidal groups were negative on Roentgen ray but positive clinically. At operation, polyps were found in both ethmoidal groups.

CASE C8.—The left ethmoidal group, negative on Roentgen ray but positive on clinical examination, was found to contain polyps at operation.

This was, however, not a constant error, for the reverse occurred in this patient:

CASE B16.—The right ethmoidal group, positive on Roentgen ray but negative clinically, was found to contain polyps at operation.

On the other hand, the roentgenologist reported as pathologic two ethmoidal groups which were found normal at operation:

CASE M14.—The left ethmoidal group, positive by Roentgen ray but negative clinically was found normal at operation. There was other sinus disease present.

CASE G4.—The right ethmoidal group was the only suspected sinus on Roentgen ray examination, while the clinical examination was entirely negative. At operation, no evidence of disease was found.

It is possible that in the latter instance the Roentgen ray findings were the result of permanent change in the sinus wall or mucosa, due to preëxisting but no longer active disease.

In addition to the above errors by the roentgenologist, reference must be made to errors in some of his attempts to interpret as well as describe some of the abnormalities seen in films. In four instances, he reported the change as due to "thickened mucous membrane," a report which might not be considered as evidence of active disease and might therefore deter the surgeon from intervening. Yet in all four instances, frank pus was found at operation:

CASE S1.—Both ethmoidal groups were reported positive clinically but the Roentgen ray reported only "thickened mucous membrane." At operation, frank pus was found.

CASE B12.—Both ethmoidal groups, positive clinically, were reported by the roentgenologist as showing merely "thickened mucous membrane." Frank pus was found in both groups at operation.

The clinical error in the ethmoidal group lay wholly in the matter of overlooking active sinus disease, an error that was demonstrated 17 times (24.3 per cent). All 17 had given positive Roentgen ray findings. In some of these there was frank pus in the sinuses but no secretion was present within the nose.

The importance of making repeated clinical examinations in such cases before giving a negative report is obvious. In some instances the Roentgen ray shadow was found to be due to polypoid degeneration of the sinus mucosa. No normal ethmoidal sinuses were wrongly called diseased. The following are illustrative cases:

CASE C2.—The right ethmoidal sinuses, negative clinically but positive on Roentgen ray, contained pus at operation. There was additional extensive sinus disease. The clinical history was one of asthma of many years' standing.

CASE T9.—Both ethmoidal groups, negative clinically but positive on Roentgen ray, were found to contain frank pus at operation. The patient had had chronic bronchitis for years and asthma for two years.

CASE S10.—Both ethmoidal groups, negative clinically but positive on Roentgen ray, showed pus at operation.

CASE B16.—The right ethmoid group was negative clinically but positive on Roentgen ray at operation, polyps were found in the ethmoidal cells.

The Roentgen ray examination of the ethmoidal sinuses is obviously much more accurate than the clinical method.

*Sphenoidal Sinuses.* The operative proof of sphenoidal disease, as in the case of the ethmoidal sinuses, was based on good evidence: the finding of polyps, pus or grossly abnormal secretions. No microscopic examinations were made.

The Roentgen ray missed only 2 of 20 diseased sinuses, an error of 10 per cent. In one of these the error may be explained by the fact that the film was misinterpreted, in that a shadow in the spheno-ethmoid region was attributed only to the ethmoidal cells and not also to an overlapping sphenoidal sinus:

CASE M14.—The right sphenoidal and ethmoidal cells were reported diseased clinically, only the right ethmoidal cells by Roentgen ray. At operation, pus was found in both the right sphenoidal and ethmoidal sinuses.

The next case is the only instance in which both the clinical and the Roentgen ray examination failed to find a diseased sphenoidal sinus:

CASE S13.—The right sphenoidal sinus was declared negative both clinically and by Roentgen ray. After a right middle turbinectomy the nasopharyngoscope showed pus coming from the sphenoidal ostium and the sinus when opened was found to contain pus.

The clinical examination was wrong in six instances, an error of 30 per cent. Five times a chronic disease was overlooked, an error due once to the absence of pus in the nose, once to ascribing pus drainage only to posterior ethmoidal disease, and twice to the presence of polyps. Four of the five had given positive Roentgen ray findings; the fifth had been overlooked in both examinations (Cases S13 above cited). In one instance, a normal sphenoidal sinus was called "diseased," through wrongly attributing pus of ethmoidal origin to both sphenoidal and ethmoidal cells.

Again the Roentgen ray examination gave more accurate results.

*Maxillary Sinuses.* Here both the discrepancies between the findings of the two methods and the alleged percentages of error are amazing. The roentgenologist, while overlooking only 3 diseased antra (2.6 per cent), is said to have reported 50 normal antra as being pathologic, an error of 45.6 per cent. Nor did the clinical examiner seem to do much better: he overlooked 10 diseased sinuses (9.1 per cent) but is alleged to have called 38 normal sinuses diseased, an error of 34.5 per cent.

These figures, we are sure, are incorrect. The error arose from the fact that the clinician in 31 instances based his opinion "normal sinus" on the fact that he obtained no evidence of disease on irrigation of the antrum. This is absolutely fallacious. It is a well-established fact that antrum washings will be returned clear in case of antral polyps, thickened diseased mucosa or in the presence of inspissated secretion. Hirsch<sup>1</sup> has reported 15 cases of chronic maxillary sinus disease, proven by open operation, in all of which irrigation had first given negative findings. One of our patients with antral polyps is a case in point:

CASE B22.—Both maxillary sinuses were reported diseased by Roentgen ray and were opaque on attempted transillumination. Both sinuses were irrigated with negative results. Upon our insistence that the antra be openly explored, this was done and both sinuses found filled with polyps.

Yet in spite of this and similar instances we were often (31 antra) unable to convince the otolaryngologist of the necessity of actual opening of all suspicious antra. Had this been done, the alleged percentage of error of both Roentgen ray and clinical examinations, especially the former, would have been materially reduced. In fact, Eadie,<sup>2</sup> in 70 cases in which the radical Caldwell-Luc operation was performed, found the Roentgen ray wrong in only one instance. It is, however, highly probable that he did not operate on borderline cases in which Roentgen ray error would be much more likely to occur.

However, a sufficient number of sinuses were adequately studied to give convincing evidence that there is a distinct Roentgen ray as well as a clinical error.

The Roentgen ray error may be due to overlooking active disease, especially in the acute earlier stages, as in this patient:

CASE W11.—The right maxillary sinus, negative on Roentgen ray but positive clinically, at operation contained pus. This patient had fever and leukocytosis.

Much more significant are those cases in which a positive Roentgen ray finding was not corroborated on open operation. In some instances, the Roentgen ray report was "cloudy," as in this patient:

CASE R19.—The right maxillary sinus was "cloudy" to Roentgen ray and did not transilluminate normally. Yet open operation showed no abnormality and examination of the interior of the antrum by the antroscope disclosed no abnormality of the mucosa.

Or the Roentgen ray finding was stated as "thickened mucous membrane:"

CASE B12.—Both antra were reported by Roentgen ray to show "thickened mucous membrane;" both were negative clinically. Neither operation nor inspection with the antroscope disclosed any abnormality in content or mucosa.

Such cases, we feel, show conclusively that a positive Roentgen ray finding may be obtained in the absence of active disease. Both patients, R19 and B12, had long histories of sinus disease and at the time of study had active trouble in other sinuses. It is quite probable, therefore, that the antra referred to had been the site of infection at some previous time, an infection which produced a permanent change in the sinus, probably with bony alteration from periosteal involvement: permanent change which in both instances

gave and always will give an abnormal Roentgen ray film, and, in Case R19, sufficient to give abnormal transillumination findings.

A further relative error in Roentgen ray findings was quite common in the antrum reports. In the case of the maxillary sinuses the roentgenologist most often attempted to interpret his findings in terms of pathologic processes: "thickened mucous membrane," "polyps," and at times these diagnoses were correct. They were, however, incorrect in sufficient numbers to make it hazardous to give them routine credence, especially, if, in the absence of clinical findings, one is tempted to consider a "thickened mucous membrane" report as probably indicative of a sinus not actively diseased. For instance, an acute flare-up with frank pus in such a sinus with "thickened mucous membrane" may fail for a time to give Roentgen ray evidence of the additional change. On the other hand, definite Roentgen ray clouding was found to occur in the presence of thickened mucous membrane alone, without evidence of any additional disease. The latter cases were demonstrated in part by Roentgen ray after lipiodol injection. (The lipiodol injections were made by Dr. Karl M. Houser of the Department of Otolaryngology.)

CASE O3.—Both antra were reported cloudy on Roentgen ray and hazy to transillumination. Films after lipiodol injection showed thickened mucous membrane.

CASE P5.—Both antra were reported cloudy on Roentgen ray, negative clinically. Films after lipiodol injection showed thickened mucous membrane. Operation showed no additional pathologic change.

CASE M14.—Both antra were reported cloudy on Roentgen ray, questionable by transillumination. Films after lipiodol injection showed thickened mucous membrane. Operation showed no evidence of active disease. The patient did have pus in the right ethmoidal and sphenoidal sinuses.

There was also a very definite clinical error, distinctly greater than that of the Roentgen ray examination. The chief pitfall for the unwary clinical examiner seemed to be in the interpretation of transillumination findings. In a number of instances a sinus clear on transillumination was found at operation to contain pus:

CASE S17.—Left antrum, cloudy on Roentgen ray, but negative on clinical examination, contained pus at operation.

CASE P20.—Both antra, reported cloudy on Roentgen ray but negative on clinical examination, contained pus at operation.

CASE A21.—Right antrum, positive by Roentgen ray but negative clinically, was found filled with pus at operation.

Several antra, filled with polyps, gave normal transillumination findings:

CASE B23.—Both antra were cloudy to Roentgen ray but negative clinically, yet at operation both were full of polyps.

CASE J24.—Both antra were hazy to Roentgen ray but transilluminated normally. The surgeon had to be urged to open the antra, which he found filled with polyps.

Inspissated secretion may likewise be overlooked:

CASE G15.—The right antrum was cloudy by Roentgen ray but on two occasions it was shown to transmit light normally. The rhinologist insisted that the Roentgen ray findings must be due to thickened mucous membrane and at first refused to open the sinus. He eventually did so, and was surprised to find it filled with a gelatinous mass of secretion that could be pulled out of the sinus in a single lump. The material gave a practically pure culture of streptococcus.

Thickened mucous membrane, the result of former disease, or bony change of similar origin, may alter transillumination findings as well as those on Roentgen ray examination, and in the absence of active disease, as in case R19, cited above. Finally, variations in bone thickness may give rise to confusion. The following may be a case in point:

CASE S18.—Both antra were negative to Roentgen ray but both transmitted light poorly. At operation, both were found normal.

Pratt<sup>3</sup> has pointed out that while positive findings on transillumination always merit full investigation, negative findings do not rule out sinus disease; that due allowance must be made for the degree of illumination to be expected in persons with thick bones as compared with fair-skinned, thin-boned individuals; and that in patients who have had one or more previous attacks of sinusitis the sinus will often show varying degrees of diminished light transmission in the absence of secretion in the sinus.

It would seem justifiable, therefore, to conclude that positive findings may be obtained both by Roentgen ray and by clinical examination in the absence of active sinus disease. These positive findings are probably due to permanent changes in the sinus walls effected by preëxisting disease. On the other hand, either method of examination may fail to find active disease, the Roentgen ray tending to miss recent acute infection, while the clinical examination may be misleading in those chronic cases in which transillumination findings are negative. The Roentgen ray error is distinctly less than that of the clinical examination. It is, however, unwise to accept as fully credible the attempts to make a definite pathologic diagnosis from the Roentgen ray film.



## PART II.

The observations set forth in Part I of this paper justified the suspicion that in sinus examinations, especially by the Roentgen ray, the evidence of past disease as well as present was being picked up. Moreover, our figures of incidence of sinus disease in bronchial asthma, while actually very high, had no absolute value unless they could be compared with figures from a series of non-asthmatics. For these reasons a control series of so-called "normals" was studied.

**Material.** Fifty patients in the medical wards of the hospital were selected who gave (*a*) no history of recent respiratory disease, (*b*) no history of susceptibility to colds, (*c*) no history of frank sinus disease in the past, and (*d*) whose ages fell proportionately into the same decades as those of the 200 asthmatics. A group so selected may well be considered as better than any average group of 50 individuals. In three of the control group, the clinical diagnosis and history (one case of infectious arthritis, one case of acute nephritis with a previous history of otitis media, one case of cervical adenitis) might have justified a suspicion of possible sinus disease acting as a focus of infection. In all three, however, the clinical examination was negative, and in only one, the nephritic, did the roentgenologist report one diseased and one suspicious sinus. The medical diagnoses of the other 47 of the control groups were diabetes mellitus (5), functional gastric disease (5), duodenal ulcer (4), arteriosclerosis (3), suspected hyperthyroidism (3), hyperthyroidism (2), pernicious anemia (2), neurasthenia (2), chronic myocarditis (2), and one each of gastric cancer, chronic appendicitis, adhesions, constipation, gall bladder disease, cirrhosis, amoebic dysentery, Banti's disease, thyroidectomy convalescent, chronic valvulitis, angina pectoris, aneurysm, renal calculus, arteriolar nephritis, nephrectomy convalescent (neoplasm), epilepsy, chorea, tertiary lues, urticaria.

Table VIII gives the age incidence by decades of the asthmatic patients and the control group.

TABLE VIII.—AGE GROUPS.

Years.	Asthmatics, number of cases.	So-called normals, number of cases.
4 to 10 . . . . .	8	2
11 to 20 . . . . .	15	4
21 to 30 . . . . .	35	9
31 to 40 . . . . .	44	11
41 to 50 . . . . .	43	10
51 to 60 . . . . .	40	10
61 to 70 . . . . .	12	3
71 to 80 . . . . .	2	1
81 . . . . .	1	0
Total . . . . .	200	50

The persons in the control group were first subjected to a clinical examination of the paranasal sinuses and were then examined by the Roentgen ray. Neither the otolaryngologist nor the roentgenologist was told that the patients in question were supposed to be "normal."

**Examination Findings.** A summary of the clinical and roentgenologic examination findings in the control group is given in Table IX. The figures are in terms of number of patients. The findings in the 200 asthmatics are placed in parallel columns for comparison.

TABLE IX.

	"Normals."		Asthmatics.	
	Number of patients.	Per cent.	Number of patients.	Per cent.
Total individuals examined . . . . .	50	....	200	
Roentgen ray examination positive . . . .	36	72.0	161	80.5
Clinical examination positive . . . . .	13	26.0	134	67.0
Clinical and Roentgen ray involvement (partial and complete agreement) . . . .	10	20.0	123	61.5
Both Roentgen ray and clinical examinations completely negative . . . . .	11	22.0	27	13.5
Complete disagreement:				
Roentgen positive; clinical negative . .	24	48.0	40	20.0
Roentgen ray negative; clinical positive	3	6.0	10	5.0

The findings are rather surprising. In the first place, the incidence of Roentgen ray evidence of sinus disease is almost as high in the control group (72 per cent) as in the asthmatics (80.5 per cent). On the other hand, the clinical evidence of sinus involvement is much lower in the "normals" or control group (26 per cent) than in the asthmatics (67 per cent). There is consequently a much greater percentage of total disagreement in the findings of the two methods of examination (54 per cent). Eighty-nine per cent of this disagreement is represented by positive-Roentgen ray, negative-clinical patients. In only 3 of the 50 persons examined were positive-clinical, negative-Roentgen ray findings, observed: two were reported to have "suspicious" ethmoidal sinuses, and one "suspicious" antra.

None of these 50 patients had any definite symptoms referable to sinus disease, yet only 11 of the 50 were negative by both examinations. It was, of course, out of the question to subject these patients to operative investigation of the suspected sinuses, so that we have no final check on the accuracy of these findings. It would seem reasonable to suppose, however, that in many, perhaps most instances, the positive findings were due to sinus disease in the past, not active in the present. In other words, sinus disease seems to tend to produce in most cases permanent changes in the sinus

mucosa or periosteum (bony change) or both, which will thereafter usually be evident in the Roentgen ray film and not infrequently on clinical examination (transillumination). A statement by Keith<sup>4</sup> is significant: "We have seen many cases of almost total absence of the frontal sinus with a very definite history of a sinus infection in childhood. There is little doubt that a severe infection of the nasal accessory sinuses in childhood may result in an arrest in the development of any of the sinuses."

It is also obvious that sinus disease is a very common condition that at one time or another affects the majority of the population in this particular part of the world. Nor is this really to be wondered at, in view of the great frequency of upper respiratory infection with us.

In Table X are given the figures for positive findings in individual sinuses as reported by the roentgenologist and the rhinologist. There is no implication of agreement between the two sets of figures.

TABLE X.—SO-CALLED "NORMAL" GROUP. INDIVIDUAL SINUS INVOLVEMENT AS REPORTED:

	(A) by Roentgen ray examiner.		(B) by clinical examiner.	
	Number.	Per cent.	Number.	Per cent.
Right frontal .	29 (1 absent)	58.0	4	8.0
Left frontal .	27 (2 absent)	54.0	3	6.0
Right ethmoid .	19	38.0	5	10.0
Left ethmoid .	21	42.0	3	6.0
Right sphenoid .	7	14.0	1	2.0
Left sphenoid .	7	14.0	1	2.0
Right antrum .	19	38.0	9	18.0
Left antrum .	19	38.0	8	16.0

(These figures do not imply agreement between Roentgen ray and clinical findings.)

In Table XI the clinical and Roentgen ray reports in the control group are recorded in terms of the number of patients affected. The corresponding figures in the asthmatics have been added for ease of comparison. There is again no implication of agreement between the two methods of examination.

TABLE XI.—SO-CALLED "NORMAL" GROUP. SINUS-GROUP INVOLVEMENT AS REPORTED:

	(A) By Roentgen ray examiner.		(B) By clinical examiner.	
	Number.	Per cent.	Number.	Per cent.
Patients with frontal sinus disease	29 ( 91)*	58 (45.5)*	4 ( 52)*	8 (26.0)*
Patients with ethmoid sinus disease	24 (114)	48 (57.0)	5 ( 72)	10 (36.0)
Patients with sphenoid sinus disease	7 ( 36)	14 (18.0)	1 ( 23)	2 (11.5)
Patients with maxillary sinus disease	24 (132)	46 (66.0)	10 (105)	20 (52.5)

(These figures do not imply agreement between Roentgen ray and clinical findings.)

\* The figures in parentheses, giving the findings in the 200 asthmatics, Table III, have been placed here for easier comparison.

There are certain differences in the two groups in the incidence of involvement of the various sinuses. The Roentgen ray findings in asthmatics showed maxillary sinus involvement most frequent (66 per cent), while in the control group frontal sinus findings were most common (58 per cent). In both groups, Roentgen ray evidence of ethmoidal involvement is next in frequency and in nearly the same percentage. In the asthmatics, frontal sinus findings rank third, with 45.5 per cent, while in the controls antrum involvement is third, with 46 per cent. On clinical examination, the order of frequency of involvement is the same in both groups, antra leading, with ethmoidal, frontal and sphenoidal involvement following in the order mentioned. In each instance the control-group percentages are less than one-third of the corresponding figures for asthmatics.

We next compared the number of sinuses involved per patient in the asthmatics and in the control group. If each main sinus or sinus group is counted as 1, and if a patient had both antra, both frontal sinuses, both ethmoidal and both sphenoidal groups involved, that is, a pansinusitis, his sinus-involvement figure would be 8. If he had only the right ethmoidal group affected, the figure would be 1. In Table XII are given the sinus-involvement figures for the two groups.

TABLE XII.—AVERAGE NUMBER OF SINUS GROUPS INVOLVED PER PATIENT IN THOSE SHOWING SINUS DISEASE.

By Roentgen ray	I. Asthmatics . . . . .	4.14
	II. "Normals" . . . . .	3.98
By clinical	I. Asthmatics . . . . .	3.42
	II. "Normals" . . . . .	2.34

The degree of involvement as determined by Roentgen ray was practically the same in the two groups. The clinical findings, however, showed a distinctly lower degree of involvement in the control group.

In order to see if the age of the individual had any bearing on the incidence of sinus involvement in the two groups, the figures were tabulated, Roentgen ray findings for both groups being given in Table XIII, and the clinical findings for both groups in Table XIV. The figures are in terms of number and percentage of patients involved in each decade. In addition, the number of sinuses affected per person has been given in columns 7 and 13 of the two tables.

Age seems to have no particular influence on the incidence of Roentgen ray findings in either group. Except for the first two decades of life, the same seems to be true for the clinical findings. No evidences of sinus involvement were found clinically in the 6 individuals under twenty years of age in the control group. The number of persons examined is, however, so small, and the difficulties of examination particularly great in these young patients, that one is not justified in attaching any particular significance to these figures.

TABLE XIII.—AGE INCIDENCE OF ALL ROENTGEN RAY FINDINGS.

Age.	Normals.						Asthmatics.					
	No. of persons (2)	Sinuses normal (3)	Per cent (4)	One or more sinuses diseased (5)	Per cent (6)	Average number of sinuses affected (7)	No. of persons (8)	Sinuses normal (9)	Per cent (10)	One or more sinuses diseased (11)	Per cent (12)	Average number of sinuses affected (13)
1 to 10	2	0	0	2	100.0	1.5	8	1	12.5	7	87.5	2.1
11 to 20	4	1	25.0	3	75.0	4.3	15	4	36.6	11	73.3	5.1
21 to 30	9	1	11.1	8	88.9	4.0	35	11	31.4	24	68.5	2.9
31 to 40	11	4	36.3	7	63.7	2.9	44	8	18.1	36	81.8	3.9
41 to 50	10	2	20.0	8	80.0	4.1	43	7	16.2	36	83.7	4.2
51 to 60	10	3	30.0	7	70.0	4.8	40	7	17.5	33	82.5	4.7
61 to 70	3	3	100.0	0	0	0	12	0	0	12	100.0	5.6
71 to 80	1	0	0	1	100.0	8.0	2	1	50.0	1	50.0	6.0
81	0	..	.....	..	.....	...	1	0	0	1	100.0	6.0

TABLE XIV.—AGE INCIDENCE OF ALL CLINICAL FINDINGS.

Age. (1)	Normals.					Asthmatic.						
	No. of persons (2)	Sinuses normal (3)	Per cent (4)	One or more sinuses diseased (5)	Per cent (6)	Average number of sinuses affected (7)	No. of persons (8)	Sinuses normal (9)	Per cent (10)	One or more sinuses diseased (11)	Per cent (12)	Average number of sinuses affected (13)
1 to 10	2	2	100.0	0	0	0	8	3	37.5	5	62.5	2.4
11 to 20	4	4	100.0	0	0	0	15	6	40.0	9	60.0	4.2
21 to 30	9	7	77.8	2	22.2	2.5	35	12	34.3	23	65.6	2.8
31 to 40	11	7	63.7	4	36.3	1.2	44	19	43.1	25	56.8	3.2
41 to 50	10	6	60.0	4	40.0	4.1	43	15	34.8	28	65.1	3.8
51 to 60	10	8	80.0	2	20.0	1.5	40	8	20.0	32	80.0	3.4
61 to 70	3	1	33.3	2	66.7	2.0	12	2	16.6	10	83.3	4.5
71 to 80	1	0	0	1	100.0	1.0	2	1	50.0	1	50.0	4.0
81	0	..	.....	..	.....	...	1	0	0	1	100.0	2.0

**Summary.** Independent clinical and Roentgen ray examinations of the paranasal sinuses were made in a series of 200 patients with bronchial asthma. While a high incidence of sinus disease was found both by Roentgen ray (80.5 per cent) and clinically (67 per cent), there was extensive disagreement between the findings of the two examinations in individual sinuses: 33.2 per cent in the ethmoidal, 29.5 per cent in the frontal, 27 per cent in the maxillary and 17.2 per cent in the sphenoidal sinuses. In order to explain these discrepancies, operative check was carried out whenever possible. Unfortunately, no frontal sinuses came to operation. In the ethmoidal sinuses a Roentgen ray error of 14.3 per cent was due chiefly to the failure to find relatively acute involvements and polypoid disease, or to confusion of overlapping sinus areas. A clinical error of 24.3 per cent was due to failure to recognize chronic disease. In the sphenoidal sinuses a Roentgen ray error of 10 per cent and a clinical error of 30 per cent were due to practically the same causes as in the ethmoidal group. In the maxillary sinuses, figures of alleged error for the Roentgen ray of 48.2 per cent and for the clinical examination of 43.2 per cent (errors largely attributed to calling a normal sinus diseased) are greatly vitiated by inaccurate and inadequate operative check, especially the determination of the state of an antrum merely by irrigation. In a sufficient number of adequate studies, however, both methods of examination were shown to be in error, chiefly in the finding by both methods of evidences of disease past, not present, also in the failure of Roentgen ray to find acute recent infection, and in the clinical failure to find chronic disease because of the fallacies of transillumination.

Clinical and Roentgen ray examinations of a control group without a history of recent respiratory infections or history of sinus disease showed a Roentgen ray incidence of sinus involvement of 72 per cent and a clinical incidence of 26 per cent, the number of sinuses per person on Roentgen ray examination being practically the same in asthmatics and controls. These findings are considered further evidence that sinus disease tends to produce permanent structural change which will often be found by Roentgen ray and at times on clinical examination, long after the disease itself is over. The age of the patient did not seem to have any material influence upon the incidence of positive clinical or Roentgen ray findings in asthmatics or controls.

**Conclusions.** 1. Neither the Roentgen ray nor the clinical examination of the paranasal sinuses is 100 per cent accurate, or comes anywhere near it.

2. Of the two, the Roentgen ray is the more sensitive, especially in the study of the ethmoidal and the sphenoidal sinuses.

3. The Roentgen ray examination will pick up the evidences of sinus disease past as well as present: a positive Roentgen ray finding therefore, does not imply clinically active disease.

4. The attempt to interpret Roentgen ray findings in terms of pathologic change (thickened mucous membrane, polyps) may be misleading, since the alleged diagnosis is not infrequently erroneous.

5. The Roentgen ray examination will often overlook acute recent sinus infection.

6. The clinical examination alone is able to give positive proof of active sinus disease, and that only if pus be seen coming from the ostium of the sinus.

7. The clinical examination frequently overlooks chronic disease, especially of the ethmoidal and sphenoidal groups, if there is no abnormal secretion in the corresponding drainage areas, and the mucous membrane as seen by the nasopharyngoscope shows little if any change.

8. It is, therefore, desirable that patients with suspected chronic sinus disease be reexamined several times before a negative clinical opinion is given.

9. The clinical examination will find at times the evidence of past sinus disease, although not as frequently as the Roentgen rays.

10. Transillumination findings are at times fallacious: polyps or mucoid secretion may transmit light normally; pathologic change due to former sinus disease or normally thick bone may be wrongly interpreted in terms of active disease.

11. Neither method is, therefore, to be relied upon alone: both must be used routinely in the study of patients with suspected sinus disease.

12. A positive finding in suspected chronic cases by either method of examination justifies the statement that a sinus *may* be, but not that it *is* actively diseased, except in the presence of pus or polyps.

13. In asthmatics a positive finding by either method of examination not only justifies but indicates the opening of the affected sinus.

14. Sinus disease is extremely prevalent in patients of all ages in this vicinity.

15. Age is apparently not a material factor in the incidence of sinus disease.

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SYSTEMIC HISTAMINE-LIKE REACTIONS IN ALLERGY DUE  
TO COLD.\*

## A REPORT OF SIX CASES.

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MANY persons are hypersensitive to various foreign agents, and display a diversity of signs and symptoms when they are in contact with the specific agent to which they are hypersensitive. The signs and symptoms depend largely on the patient's degree of sensitiveness, the mode of contact with the offending agent and the dose. Very little is known concerning either the physical or chemical characteristics of agents which can sensitize human beings, and the pathogenesis of the local and general reaction is imperfectly understood. Factors such as light, heat, cold, and many varieties of vegetable and animal matter are known to provide allergic reactions in man.

As pointed out by Duke, the reactions caused by physical agents fall into two groups: those in which the reaction is confined to the area directly exposed to the physical agent, and those in which there is not only local, but also resulting systemic reaction. Various theoretic explanations have been offered for both types of reactions, the most significant of which seems to be that suggested by Lewis and his associates and by Duke. They believe that patients with allergic tendencies may become specifically hypersensitive to some new body formed in the tissues, solely under the influence of one specific physical agent, such as certain rays of light, heat or cold of certain specific grades, or possibly other analogous physical agents. This new substance apparently may produce either a local or a systemic reaction. Lewis and Harmer believe that in urticaria factitia a substance which has a histamine-like reaction is released in the skin and gradually passes into the general circulation, there to exert a general effect. Harris has demonstrated that alcoholic extracts of normal skin of human beings contain a substance which, when introduced into the normal skin of a subject, by puncture, causes areas of flushing and wheals. It is well known that physical agents may cause an aggregation of protein molecules and other physiochemical changes in protein *in vitro*. Assuming that such

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changes can take place *in vivo*, one may easily conceive that patients with allergic tendencies, possibly constitutional, may become specifically hypersensitive to a body formed in this way and may react with urticaria and asthma, just as they do on suitable contact with pollen.

The strange clinical syndrome associated with sensitiveness to cold has been discussed by many observers, particularly by Duke, who has studied especially the local disturbances of the skin resulting from physical agents, such as light, heat and cold. He has noted, in 2 cases, total collapse following unusual exposure to cold. Ward reported the case of a patient who was so sensitive to cold that exposure of her face for a few moments to a cold wind resulted in blanching and stiffness of the skin as if it were frozen. Osler and Fraser reported cases in which patients had urticaria if exposed to low temperature. Jodassohn and Schaaf reported 2 cases, in the same family in which there was formation of wheals following exposure to cold weather. This response was noted only on the flexor surfaces of the arms and legs.

The present report is based on the studies carried out on 6 subjects, 3 of whom were patients at The Mayo Clinic. All exhibited disturbances of the skin and systemic reactions following exposure to moderate grades of cold. The reactions were so similar in these cases as to constitute a most striking clinical syndrome, which, to our knowledge, has never been reported.

**Report of Cases.** CASE I.—A Jewish woman, aged forty-nine years, entered The Mayo Clinic October 17, 1927, complaining of attacks of swelling of the hands and stomach trouble. For three years the hands had become swollen following exposure to cold, particularly after immersion in cold water or after the removal of articles from the refrigerator. After the hand had been removed from cold water, the area which had been immersed gradually became heavy with edema, associated with a prickly sensation; then a sharp rise in the surface temperature occurred, associated with a sensation of burning. This was followed by a sharp systemic reaction, with flushing of the face and a sensation of weakness. The general reaction passed in about twenty minutes, although the disappearance of the local swelling required about twenty-four hours.

The patient was moderately obese. On admission, the systolic blood pressure was 135 and the diastolic 98; the pulse was 70 and the temperature 98° F. The acidity of the stomach was normal and roentgenograms of the stomach and gall bladder were negative. All of the laboratory reports were negative. Experiments were carried out on five successive days.

Experiment 1: The hand was immersed in water at 10° C. for ten minutes. Systemic reaction or changes in the hand and forearm were not observed while the hand was in the water. When it was removed, it looked blanched. There were no subjective symptoms except those of coldness and numbness in the extremity. At the end of two minutes the hand began to itch and burn. At the end of three or four minutes, it turned red and started to swell, became firm, and felt hot. At the end of five or six minutes, the face was flushed and became scarlet; the patient was conscious of burning and throbbing in the swollen area, and of cardiac palpitation. The pulse rose rapidly; there was a drop in the blood pressure at the height of the

reaction (Figs. 1 and 2). An occasional premature contraction was noted, and in the electrocardiogram was an inverted *T* wave in Lead III, which was absent during the control period. The systemic reaction passed off in from

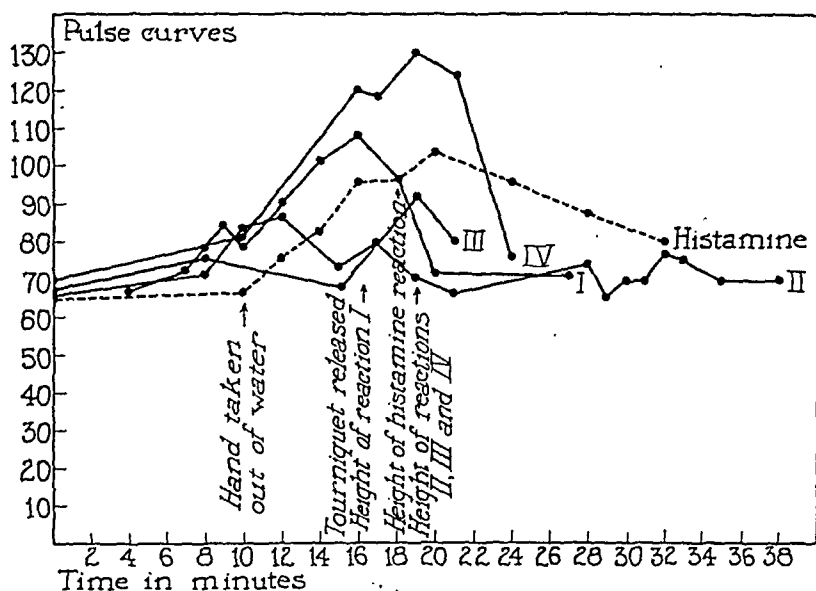


FIG. 1.—Histamine-like systemic reaction produced by immersion of hand in water at 10° C. for a period of ten minutes. The sharp increase in pulse rate and the parallelism to the rise in pulse rate obtained after the administration of 0.5 mg. of histamine subcutaneously is shown by the dotted line.

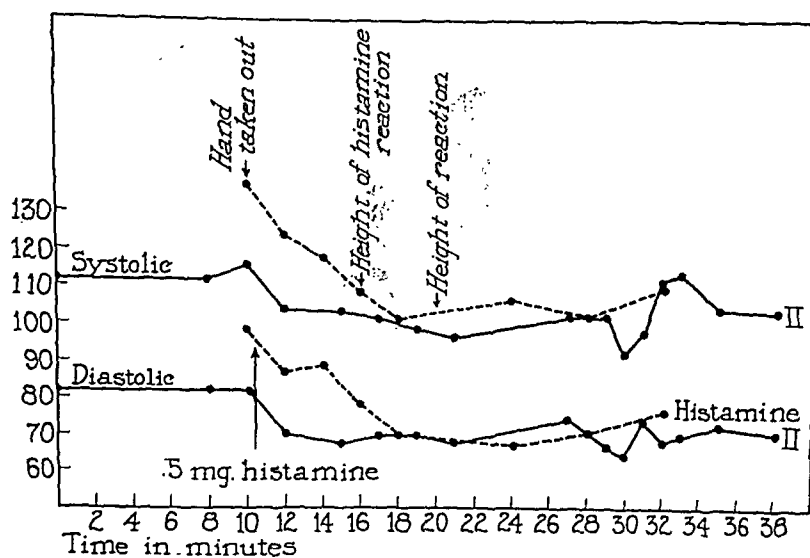


FIG. 2.—Histamine-like systemic reaction produced by immersion of hand in water at 10° C. for ten minutes, illustrating drop in systolic and diastolic blood pressure. The parallelism of this reaction to the response of blood pressure following the injection of 0.5 mg. of histamine subcutaneously is shown by the dotted lines.

twenty to twenty-five minutes. The hand was markedly swollen with a sharp line of demarcation between the swollen and normal tissue (Fig. 3). The patient was unable to close the hand. The edema was of a nonpitting type and serum did not exude from the hand when the subcutaneous tissue

was punctured. The swelling gradually disappeared in eighteen to twenty hours. Changes in color or tension in the skin were not noticed following the subcutaneous injection of solution of pituitary (U. S. P.) into the swollen region. Local or systemic reaction did not occur when the foot was immersed in cold water for a similar period.

Experiment 2: A tourniquet was applied around the arm for ten minutes while the hand was immersed in water at  $10^{\circ}\text{C}$ ., and kept on for an additional five minutes after the hand was removed from the water. Local or



FIG. 3.—Swollen appearance of the hand after being immersed in water at  $10^{\circ}\text{C}$ . for ten minutes. The sharp line of demarcation between the normal and swollen areas is seen at the upper limit of immersion.

general reaction did not occur until the tourniquet was removed. Then an exaggerated type of local and systemic reaction followed in the usual sequence.

Experiment 3: An attempt was made to examine the blood of the patient for a chemical substance during the height of the reaction to cold. Blood was obtained from the basilic vein of the arm which had been removed from the cold water both just preceding the systemic reaction and at the height of it. The patient's serum was applied to living strips of intestine from a rabbit that were suspended in oxygenated Locke's solution. A similar test was carried out with the blood of this patient, after a known amount of histamine (0.5 mg.) was given by subcutaneous injection. The

results were negative in each experiment. Chemical tests also were negative. This is explicable since Koessler has shown that neither the biologic nor the chemical reactions are sufficiently delicate to determine the presence of histamine in dilutions such as those used in these experiments.

Experiment 4: The systemic reaction following cold was accurately reproduced by the administration of 0.5 mg. of histamine subcutaneously (Fig. 1). The flushing of the face, the increased pulse rate and drop in blood pressure were reproduced, and the patient experienced the same subjective symptoms as had followed the immersion of the hand in cold water. The systemic reaction passed off in from twenty to twenty-five minutes. The local reaction passed off in about an hour.

CASE II.—A young man, aged twenty-two years, entered the Clinic November 16, 1925, complaining of tingling and burning sensations of the body when exposed to cold. He had experienced these sensations for three months. The first attack came on after the patient had been in swimming, he fainted on his way to the dressing room. Following this, when any portion of the body became chilled, as by immersion of the hand in cold water, the exposed surface of the skin became red and swollen, and the area burned and tingled. The swelling persisted for from twelve to twenty-four hours.

The patient was well-developed and well-nourished and weighed 160 pounds. The results of general examination and routine laboratory tests were essentially negative. The following experiments were carried out:

Experiment 1: The hand was immersed in water at 10° C. for two minutes, and then was taken out. After one and a half minutes the face became slightly flushed. After two minutes, the arm was slightly red and the pulse a little weaker but accelerated. After five minutes the skin of the hand and arm became swollen, thickened, and leathery in texture, and there was a sensation of burning and bursting in the swollen region. The swelling was sharply limited to the exposed area. The face was scarlet red at this time. At the end of ten minutes the systemic reaction was over. The redness of the extremity disappeared in from thirty to sixty minutes, but traces of the swelling persisted for from twelve to twenty-four hours.

Experiment 2: The local swelling and the systemic reaction were prevented by the application of a tourniquet around the arm just above the exposed surface. After the tourniquet was removed, an unusually severe systemic reaction occurred.

Experiment 3: After the hand had been immersed in cold water, it was placed in the hand calorimeter (Stewart-Keggerries) and the elimination of heat was determined for a period of twenty minutes. The right hand, under normal conditions, liberated 0.72 small calories in twenty minutes. After being held in cold water at 13° C. for ten minutes, the same hand gave off 1.20 small calories in the same period of time. This evidence of active vasodilatation was verified by the sharp increase in the temperature of the skin as measured by the thermocouple. The capillaries of the nailfolds were normal in size and shape before the hand was immersed in the cold water. After exposure to cold, there was a definite increase in the number and width of the capillaries, whereas the rate of bloodflow was unchanged. Essentially the same local and systemic reactions were obtained when on successive days, the hand and forearm were immersed in water at 10° C. for four minutes, and when they were immersed in water at 8° C. for ten minutes.

Experiment 4: The patient was given a bath in water at 11° C. The hands, feet, legs, thighs and hips were immersed in the water for four minutes. The entire surface of the skin was scarlet; the resulting swelling was limited to the hands, feet and bridge of the nose. The thickening of the skin

practically disappeared in twenty minutes, but the redness persisted for fifty minutes. Flushing of the face was not observed. Blood pressure, pulse and mouth temperature readings were made over a period of twenty-five minutes (Fig. 4). The mouth temperature remained normal during the entire experiment. When the patient entered the bath the systolic blood pressure was 125, and the diastolic 75, and the pulse was 96. When he came out of the bath, the systolic pressure was 90, the diastolic 60, the pulse was 84, and the heart sounds were normal. The systolic blood pressure dropped to 55 at the end of twenty-three minutes, at which time the patient fainted. The pulse rate dropped to 48 beats each minute but the heart rate and rhythm were regular. We were unable to obtain the dias-

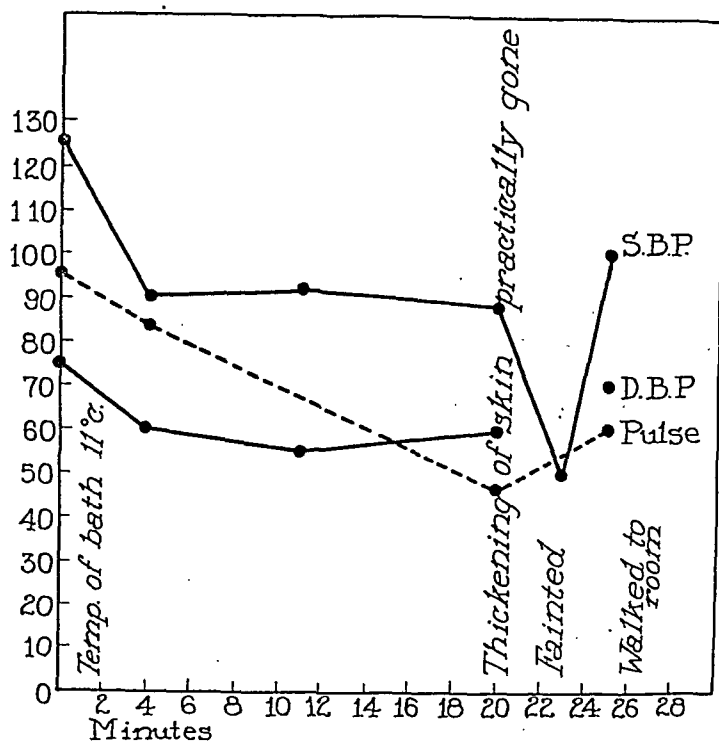


FIG. 4.—Blood pressure and pulse rate observed during partial immersion of body in water at 11° C. for four minutes. The marked drop in systolic blood pressure is shown during the height of the skin and systemic reaction, indicating a state of shock. S. B. P. =systolic blood pressure; D. B. P. =diastolic blood pressure.

tolic pressure at this point. Two minutes later the systolic blood pressure was 100, the diastolic 70, and the pulse was 60. Three minutes later the patient was able to walk to his room and felt perfectly well.

CASE III.—A boy, aged fifteen years, presented the following history: Three years prior to admission to the Clinic he was given 33,000 units of tetanus antitoxin because of a dirty wound which he had received. A few days later, irregular, raised, red and white wheals appeared over the back, shoulders, chest and thighs, following exposure to cold. Ordinary cold weather such as the patient experienced in southern Canada would bring out the reaction. The wheals usually disappeared in thirty to forty minutes, but occasionally would persist for ten to twenty-four hours. He noted the same reaction after swimming. On two occasions, after being in swimming, practically the entire surface of the skin was covered with urticarial wheals. He fainted on both occasions. A physician who was called was unable to

feel the pulse beat; the heart rate was very rapid. Hot-water bottles were applied, stimulants and hot drinks were given, and within thirty to forty minutes the patient felt perfectly well. His susceptibility to cold had gradually decreased during the last three years. He is now able to expose himself to cold weather, or even to take a cold bath without any subjective symptoms other than the appearance of the urticarial wheals.

The patient was of normal weight, height, and build for his age. The systolic blood pressure was 115, the diastolic, 70, and the pulse rate was 68 to 70 each minute. The results of general examination and laboratory tests were negative. The following experiments were carried out on two successive days.

Experiment 1: After a series of control readings of blood pressure and pulse rate, with the patient at rest, the back was stroked in the pattern of a network of lines. The reaction, manifested by redness of the pressure lines and the flare and formation of raised linear wheals, occurred promptly. Readings of the blood pressure and pulse rate were recorded at intervals of one minute for twenty minutes; there was no change in the blood pressure or pulse rate. Subjective symptoms were not experienced, and objective signs were not noted, except the linear wheals on the back due to the stroking of the skin.

Experiment 2: The patient was given a cold bath for a period of four minutes with the temperature of the water 50° C. The hips, thighs, legs and feet were immersed in the water. After getting out of the cold water he had a definite chill lasting ten minutes, but otherwise did not experience ill effects from the bath. The surface of the skin exposed to the cold water was deep scarlet, but wheals did not appear. The blood pressure and pulse rate were observed at intervals of one minute for a period of twenty minutes but there was no change in these readings aside from a slight initial rise in pulse rate (84 to 120 each minute) when the patient was first placed in the cold water.

Experiment 3: An attempt was made to determine the patient's susceptibility to histamine given subcutaneously in small doses. With the administration of 0.1 mg. of histamine, a change was not observed in the blood pressure or pulse rate, but the patient complained that his face felt hot four minutes after the administration of the histamine. His face was definitely flushed at that time. As a control, a normal person was given 0.3 mg. of histamine subcutaneously; an entirely insignificant reaction resulted. Five hours later, 0.3 mg. of histamine was given to the patient. Two minutes later, the face was scarlet, the redness extending down over the neck and chest. He complained of feeling hot around the face and head. There was a drop in blood pressure from 115 systolic and 70 diastolic, to 106 systolic and 66 diastolic, with a rise in pulse rate from 72 to 92 each minute. The local reaction consisted of a local wheal, 2 cm. in diameter, surrounded by a red area 10 cm. in diameter. Essentially the same local and systemic reaction was noted four hours later when the patient was given 0.5 mg. of histamine subcutaneously.

The diagnosis in this case was made from the history, which was similar to that of the other 2 cases. It is probable that the patient's susceptibility had lessened in the three-year period. The systemic reaction, as described by his mother, left no doubt as to the similarity of the reaction to that in the other 2 cases. The redness of the skin, wheal formation, flushing of the face, and rapid rise of the pulse, with syncope, were most indicative of the allergic reaction. The increased susceptibility to histamine, when given subcutaneously, may be an effect of the former allergic state.

Since our study of the foregoing 3 cases was made our attention has been called to three additional cases which, with the kind permission of the attending physician, we are including in our report.

CASE IV.—A married woman, aged thirty-two years, was first observed by Dr. A. I. McKinnon of Guelph, Ontario, February 14, 1928, during treatment for alcoholism. The patient had been using alcohol to excess for six months, and at irregular intervals for a longer period. She also had been in the habit of using codein and morphin, but had not used these drugs for the last two years. Her sensitivity to cold first became apparent in 1922. While she was bathing in a lake, she collapsed and after she had been taken out of the water a blotchy rash had appeared over the entire body. The following winter, if she went out on a cold day, her face and legs became sore and swollen. The condition had gradually become more severe; so that, in recent winters, if she were out in the cold for ten or fifteen minutes, her face, hands and legs would become sore, red and swollen. This condition would subside in the course of a few hours if she remained in a heated building at a normal room temperature.

Dr. McKinnon carried out the following experiment: In the patient's bed room, at ordinary room temperature (approximately 72° F.), her right arm was immersed in a basin of snow for a period of twenty minutes. At the end of this time the arm was removed from the snow and the skin was dried. The area became swollen rather rapidly, and dusky red. It was noticeably warm, and the swollen area had a sharp outline corresponding to the area covered with snow. As the swelling developed, the patient felt a sense of flushing in the face and in the other arm. The swelling continued for about an hour, at which time the surface of the skin was raised about 0.3 cm. above the surrounding area. Two hours later the swelling began to subside but it did not entirely disappear until forty-eight hours had elapsed. As the swelling disappeared, the pain became less severe.

CASE V.—A woman, aged fifty-seven years, was observed by Dr. Edmond Andrews, of Chicago. She had suffered from acute attacks of swelling of the entire right arm for a period of thirty years. The middle portion was always much more involved than the hand; and the deeper layers apparently were more involved than the skin itself, which became only slightly reddened. These attacks occurred but once or twice a year, and intensive study by a good many physicians failed to find any cause for them. Each attack lasted but a few hours, and none has occurred for five or six years. Neither the patient nor Dr. Andrews can remember whether or not they occurred during the winter months.

Five years before she sought advice, redness, swelling and itching, mostly of the skin of the thighs, had begun to occur after being in swimming. This condition had been evident but not very severe. Two years after she had noticed the condition of the thighs while swimming in very warm water at Palm Beach, and after she had been in but a few moments, she had felt a little dizzy and had come out at once. On reaching the shore she had fainted and had remained unconscious for more than an hour in spite of all efforts to restore her. This attack had not been accompanied by any skin eruption and its cause had not been diagnosed at that time. Since then, every time swimming has been attempted or even when bathing in very cold water in a tub, widespread, giant urticarial lesions have appeared on the parts exposed to the water. Each of these attacks has been accompanied by dizziness and the patient has nearly fainted if the lesions have been very marked.

At about the time when Dr. Andrews was observing this patient, following a suggestion in a report on allergy in the *Proceedings of the Staff Meetings of*

*The Mayo Clinic*, he tried out the effect of immersion in ice water of the hands of his patient. The results were the same as those reported in Case I, except that in his case there was no well-defined line of demarcation. After the extremity was immersed up to the wrists, patchy urticaria covered the arm up to the shoulder. The result of daily production of this reaction has been the establishment of an almost complete cure. The patient now can swim for fifteen or twenty minutes in an indoor pool without the production of any dizziness or urticarial lesions.

CASE VI.—A man, aged thirty years, was observed by Dr. Henry E. Palmer of Tallahassee, Florida. The patient had undergone the usual diseases of childhood: mumps, measles and pertussis. Recovery had been prompt and there were no sequelæ. He had attended the Virginia Military Institute at Lexington, Virginia, and had been graduated from the U. S. Military Academy at West Point. He always had been robust, active, and athletic and had weighed 175 pounds when he had left West Point. He had not been affected by the climate either at Lexington or at West Point. In 1925, he had begun to complain of being uncomfortably affected by cold weather in Tallahassee, where, in fall and winter, the temperature often descends to 18° or 25° above zero, Fahrenheit, but never lower. At this time his weight had been 215 pounds. He had led an active outdoor life.

In September, 1926, a party, including the patient drove to Rhodes Springs, about sixteen miles south of Tallahassee for a swim. The springs at this place, three or four in number, gush from the ground, and the water is almost as cold as ice water. After the patient had been swimming, Dr. Palmer noticed the patient scratching himself, and was impressed by the redness of the skin. After about fifteen minutes of swimming, the patient went to the dressing room, and about fifteen minutes later two men reported that a man in the dressing room was acting very strangely. Dr. Palmer found the patient still undressed, standing in the middle of the room, scratching. He was rational then. A young man, who had been in the room with the patient, stated that he had fainted and had fallen as though he were dead but that he soon had recovered, had sat up, and had fainted again. Dr. Palmer had the patient sit down, and had him partially dressed, when sudden pallor came on and he began to sway. He was laid on the bench and soon recovered. Later, a very thorough physical examination did not reveal anything abnormal.

The following experiment was carried out: A piece of ice, about 10 cm. in diameter was placed on the back of the patient for ten minutes. This caused local congestion with marked thickening of the skin over the area. Even now when the patient is exposed to a cold wind, his hands, face, and ears swell uncomfortably. He is not able to take a bath in water as cold as hydrant water, even in mid-summer. Otherwise he is active, healthy and strong.

**Comment.** The reactions in these cases were similar and constitute what we believe to be a definite clinical syndrome. It is shown that 5 of the 6 subjects had reactions after being in swimming, and we feel sure that the other subject (Case I) would have reacted in a similar manner, had she been subjected to the same experience. In Cases I and II, the reactions were strikingly similar. The local reaction during immersion in cold water consisted of pallor, and after removal of the part from the cold water, of erythema, increased heat, itching and swelling, sharply limited to the exposed surface. The reaction was brought out best by immersion of the hand or arm



in cold water between the temperatures of 10° and 15° C. Practically no reaction followed exposure of the skin to water at 20° C. Studies of the skin temperatures and rates of heat elimination of the exposed hand showed a sharp vasodilating response following exposure to cold. The systemic reaction came on uniformly from four to six minutes after the exposed extremity was removed from the cold water. This was manifested mainly by a rise in the pulse rate and a definite drop in the blood pressure, an effect not observed in normal subjects. A reflex or nervous basis for the systemic reaction seemed definitely eliminated by the period of latency (four to five minutes) in the production of the reaction and by the fact that it was inhibited by cutting off the circulation of the arm. In the second experiment in Case I, the tourniquet was applied for fifteen minutes, during the first ten of which the hand was immersed in cold water. After the hand was removed from the cold water, a reaction did not occur as long as the tourniquet remained around the arm. When it was removed, the local and systemic reactions were more severe than they had been in the previous experiments. These observations are indicative of a chemical basis for the general disturbance, for it was prevented as long as the blood was not allowed to flow out of the affected region. Similar results were also obtained in Case II.

The systemic reaction in Case I was exactly reproduced by the administration subcutaneously of 0.5 mg. of histamine. The patient was unable to distinguish between the systemic reaction as a result of histamine and that which followed exposure of the hand to cold water. The subjective symptoms were the same in both experiments. The time of onset, the duration of the reaction, and the phenomena demonstrable in pulse and blood pressure were strikingly similar. The premature contractions and the presence of an inverted *T* wave in Lead III, during the height of the systemic reaction following exposure to cold, may well be explained by the presence of histamine-like bodies liberated in the general circulation, from the exposed area; premature contractions and transient changes in the auriculoventricular conduction time have been observed following the intravenous use of histamine (Hashimoto). The studies would lead one to believe that a physical agent, such as cold, might break down certain molecules in the skin, subcutaneous tissues or muscles, with the liberation of histamine or histamine-like bodies which, when carried into the general circulation, would produce the typical histamine effects. This seems quite possible in view of the fact that the exact clinical syndrome was reproduced in one of the patients by a known dose of histamine. Abel and Kuboto stated: "What form the agent that kills or injures the cell takes, should be immaterial. Whether it be heat, mechanical injury, bacteria or their products, or pharmacologic agents that injure or destroy the cells, in every instance we should expect to find histamine

liberated. Nor need the injury necessarily be of so gross a character as to be immediately demonstrable under the microscope." Lewis and Harmer believe that in urticaria factitia a substance having a histamine-like reaction is released in the skin and gradually passes into the general circulation, there to act generally. In suitable subjects, after extensive stroking of the skin of the trunk, they observed a general reaction of the small vessels of the skin, resulting in a rise in skin temperature and a flush that was just perceptible or distinctly perceptible in the facial skin. The systolic blood pressure and pulse usually remained unchanged. Harris concluded that alcoholic extracts of normal skin contain histamine. Its amount in normal skin is estimated at about 10 mg. for each kilogram of tissue, or 1 to 100,000, the quantity varying somewhat for different regions of the body. Abel and Kuboto had previously shown that histamine is a normal constituent of liver, gastric mucosa and skeletal muscle, and they believe that it is a widely distributed constituent of all animal tissues. Thorpe has recently confirmed and extended these observations.

These cases seem to be amenable to treatment. It was believed that since the patient was sensitive to a chemical substance formed in the tissues of the body, autodesensitization would be possible. Two procedures were, therefore, considered: (1) Desensitization by repeated injections of histamine, over long periods, in doses so minute as to be insufficient to produce a systemic effect and with gradual increase in the dosage; (2) autodesensitization by allowing the patient to desensitize himself by daily immersion of the hands in cold water, decreasing in temperature and for increasing periods. The patient in Case II was advised to take cold baths daily. He did this for six months until untoward effects entirely disappeared; one year later it was reported that he was entirely cured. This regimen was carried out in Case V with practically complete recovery so that the patient now can swim for fifteen or twenty minutes in an indoor pool without dizziness or the production of urticarial lesions. The same regimen was outlined for Case III, and we believe that the patient will obtain good results following this procedure. In Case I, it was noted that after the hands were immersed daily, the reaction became less intense. Further studies, were not possible, and the patient was advised to return home and to carry out a similar regimen. It is believed that the disturbance in the other cases will disappear gradually.

It seems probable that the explanation of the disturbance known as chilblains has a similar basis. The vasodilatation reactions, with increased local heat and burning and swelling of the soles of the feet following exposure to cold are suggestive of this. Systemic reactions have not been reported. The gradual disappearance of the condition over a period of two or three years seems to indicate a mechanism of autodesensitization.

**Summary.** Six cases are reported which exhibit local and general symptoms of cold allergy. The local effects on the skin were: pallor during the period of exposure, followed by redness, swelling, and increased heat of the hands after removal from the cold. Following a latent period of three to four minutes, a characteristic systemic reaction appeared, which was characteristic of that produced by histamine. There was a fall in blood pressure, a sharp rise in pulse rate, flushing of the face, a tendency to syncope, with transitory recovery in fifteen to thirty minutes. Complete recovery from the local reaction occurred in twelve to twenty-four hours. The experimental work which was carried out gave evidence of the chemical nature of these reactions, and strongly suggested the release of a histamine-like substance in the skin following exposure to cold; this substance, when carried in the general circulation, produced a reaction characteristic of histamine. These cases are amenable to treatment. By daily immersion of the hands in cold water, decreasing in temperature, for increasing periods, excellent results may be obtained. These clinical observations are further confirmation of the work of Lewis and his associates on the presence of histamine or allied substances in the skin of human beings.

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## EPHEDRIN AS A MYDRIATIC IN CAUCASIANS.\*

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SINCE the discovery of the mydriatic action of ephedrin by Miura,<sup>1</sup> favorable clinical reports have been published by De Vriesse,<sup>2</sup> Groënouw,<sup>3</sup> Suker,<sup>4</sup> Stephenson<sup>5</sup> and Marmoiton.<sup>6</sup> They all advocated its use in the exploration of the fundus on account of the rapid action, absence of cycloplegia, short duration of mydriasis and harmlessness of the drug. Inouye<sup>7</sup> was the only one who encountered a case in which ephedrin precipitated an acute attack of glaucoma. Following the recent systematic study of ephedrin by Chen and Schmidt,<sup>8</sup> interest in its use in ophthalmology has been revived. Middleton and Chen<sup>9</sup> observed that a 10 per cent solution of ephedrin sulphate, or the same concentration with the addition of 0.1 per cent of homatropin hydrobromide, or of 0.1 per cent of atropin sulphate, may be used locally as a mydriatic for routine ophthalmoscopic examinations. Chen and Poth<sup>10,11</sup> found that ephedrin, like cocain and euphthalmin, is an efficient mydriatic for Caucasians, but of little value in dilating the pupil of the Chinese and negroes. It was shown in the same investigation that ephedrin mydriasis is about as great as cocain or euphthalmin mydriasis. Howard and Lee<sup>12</sup> also reported that ephedrin is more effective as a mydriatic in individuals with light irides than in those with dark. Dittman,<sup>13</sup> on applying a 3 per cent solution on himself, experienced conjunctivitis, increased intraocular tension, and blurring of vision. Schoenberg,<sup>14</sup> on the other hand, concluded from a study of several hundred patients that ephedrin is a valuable drug to produce mydriasis for ophthalmoscopic examinations. The same author found that the effect of ephedrin on the pupil is counteracted by pilocarpin within five to ten minutes. Similarly, Müller<sup>15</sup> after two and a half years' experience considers it as a useful agent for diagnostic purposes. This investigator administered ephedrin in several cases of chronic glaucoma, and found no change in the intraocular pressure.

The present work is a continuation of that of Middleton and Chen.<sup>9</sup> Studies were carried out on both healthy and diseased eyes, and measurements made with more precise methods. Only the data from Caucasians are presented here, since ephedrin is not a reliable mydriatic for the Chinese and negroes.

\* This investigation has been aided by a grant from the American Pharmaceutical Association Research Fund.

**Mydriasis.** In 21 normal eyes treated with a 10 per cent solution of ephedrin sulphate, the increase of the transverse diameter of the pupil in an hour in diffuse daylight varied from 1 to 3 mm., the average being 2 mm. Similarly in 10 other individuals, studied

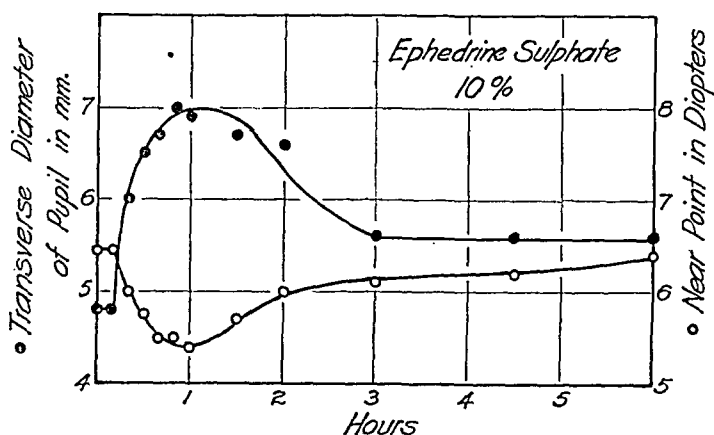


FIG. 1.—Course of ephedrin mydriasis. J. S., Caucasian, male, aged eighteen years. Observations were made on the left pupil in a dark room with a standard lamp, giving a light intensity of 13.3 candlepower, at a distance of 1 m.

under constant illumination in a dark room and with a most accurate instrument as described elsewhere,<sup>11</sup> the increase of the transverse diameter of the pupil varied from 1.1 to 3.3 mm., the average being 2.2 mm. As shown before<sup>9</sup> the onset of mydriasis takes place

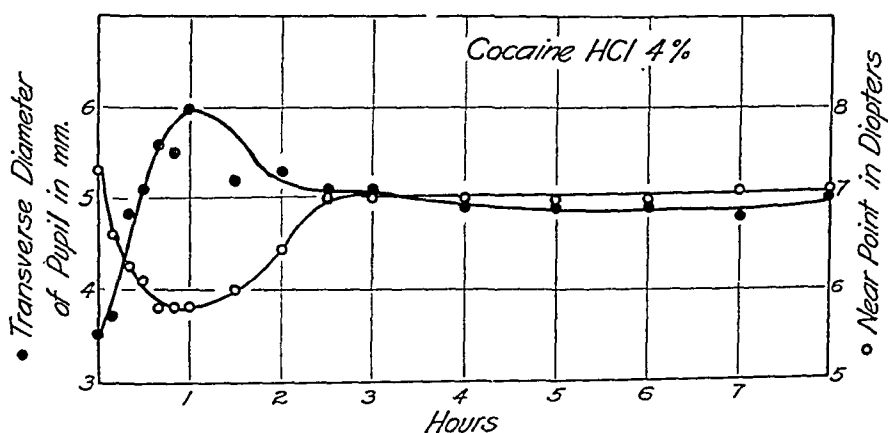


FIG. 2.—Course of cocain mydriasis. G. S., Caucasian, male, aged twenty-two years. Observations were made on the right pupil in a dark room with a standard amp, giving a light intensity of 13.3 candlepower, at a distance of 1 m.

within fifteen to thirty minutes. The maximal dilatation is attained within thirty to sixty minutes. The duration is three to nine hours. Fig. 1 shows the typical course of the mydriasis. The observations in that case were made in a dark room with a standard lamp giving a light intensity of 13.3 candlepower, set at a distance of 1 m. from

the eye being tested. Cocain and euphthalmin, studied under the same conditions, were found to produce a longer mydriasis, as shown in Figs. 2 and 3.

The light reflex in ephedrin mydriasis is active, which is a disadvantage in ophthalmoscopy, but can be remedied by the addition of a small amount of homatropin, or euphthalmin. Such solutions,

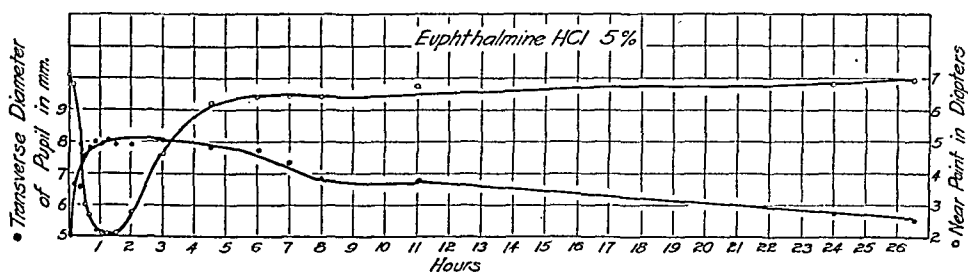


FIG. 3.—Course of euphthalmin mydriasis. P. L., Caucasian, male, aged sixteen years. Observations were made on the right pupil in a dark room with a standard lamp, giving a light intensity of 13.3 candlepower, at a distance of 1 m.

containing, for instance, 10 per cent of ephedrin sulphate, and 0.1 per cent of homatropin hydrobromid or 1 per cent of euphthalmin hydrochlorid, render the pupil very sluggish to light. The admixture of homatropin or euphthalmin makes the course more like that of cocain mydriasis, as shown in Figs. 4 and 5. The increase of the

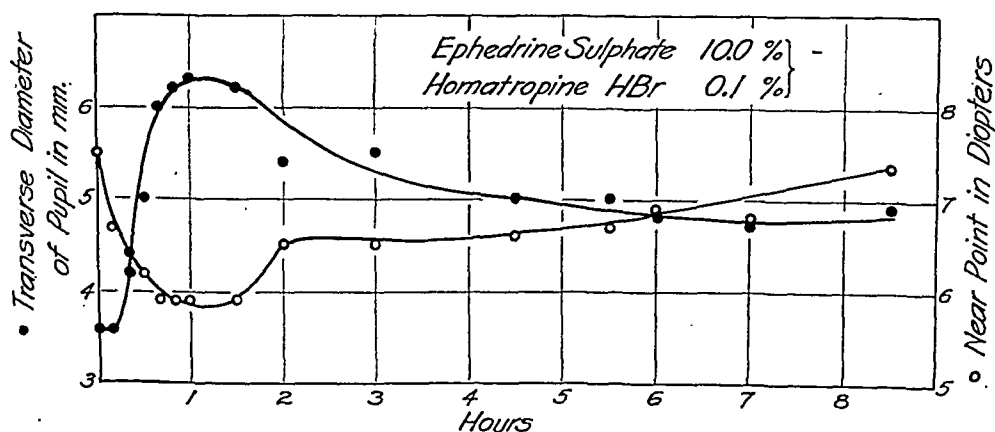


FIG. 4.—Course of ephedrin-homatropin mydriasis. G. S., Caucasian, male, aged twenty-two years. Observations were made on the right pupil in a dark room with a standard lamp, giving a light intensity of 13.3 candlepower, at a distance of 1 m.

transverse diameter of the pupil caused by ephedrin-homatropin or ephedrin-euphthalmin, in the majority of cases, is 0.5 to 1 mm. greater, and the duration longer, than that by ephedrin alone.

With the two combinations, that is, ephedrin-homatropin and ephedrin-euphthalmin in the concentrations described above, 32 pathologic eyes were studied. They include optical atrophy, neuro-

retinitis, retinitis pigmentosa, choroidoretinitis, cataract, extreme myopia, uveitis, iritis, suppurative keratitis, corneal opacity, chronic dacryocystitis, ptergium, blepharitis, and hordeolum. With the exception of uveitis and iritis cases, all the pupils dilated to the same extent as the normal, under the influence of these two solutions.

The mydriatic action of ephedrin, ephedrin-homatropin or ephedrin-euphthalmin is easily counteracted by the instillation of pilocarpin hydrochlorid. The pupil begins to contract in five to ten minutes after the application of such miotics, and returns to normal in approximately an hour.

A preliminary study was also made with solutions containing half the quantity of ephedrin, that is, 5 per cent, and the same

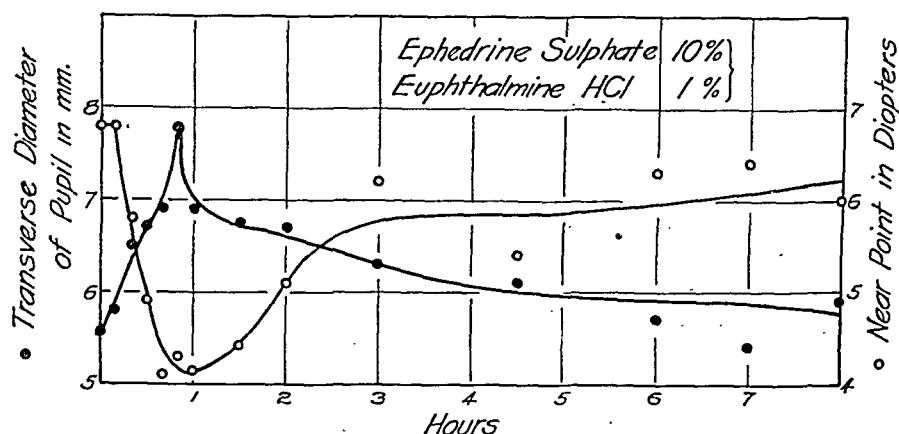


FIG. 5.—Course of ephedrin-euphthalmin mydriasis. R. G., Caucasian, male, aged twenty-one years. Observations were made on the right pupil in a dark room with a standard lamp, giving a light intensity of 13.3 candlepower, at a distance of 1 m.

quantity of homatropin or euphthalmin as mentioned above. The results are similar except that in a few cases the mydriatic action appeared to be comparatively less pronounced.

**Accommodation.** In several individuals the power of accommodation was tested by measuring the near point with an accommodation disk having in the center a vertical black line, 0.2 mm. in width, fitted on a Prince's rule. The observations were made in a dark room under constant illumination, immediately after the measurement of the pupil. The vertical line of the accommodation disk is made perceptible by a Greenberg cystourethroscope lamp, which is attached on the top, connected to a 3-volt battery, and covered by a shade so that the subject does not see the lamp. In every instance, the near point was measured from the surface of the eye, not from the anterior focus. During observation the fellow eye is covered by a patch. Examples are given in Figs. 1 to 5.

From Fig. 1, it will be seen that ephedrin caused a recession of 1.1 diopters during maximal mydriasis. With the addition of

homatropin, the near point receded by 1.6 diopters as shown in Fig. 4; and with the addition of euphthalmin, it receded by 2.7 as shown in Fig. 5. Each of the three individuals could read Jaeger's test Type II held at a distance of 25 to 30 cm. from the eye. This proves that the mydriatic action of ephedrin, either alone or in combination with homatropin or euphthalmin, does not interfere with accommodation materially. Cocain studied under the same conditions diminished the near point by 1.5 diopters (Fig. 2). Euphthalmin, on the other hand, produced a drop of 5 diopters (Fig. 3). The last individual complained of blurring of vision.

#### THE EFFECT OF EPHEDRIN SOLUTIONS ON INTRAOCULAR PRESSURE.

Solution.	Subject.			Change in intraocular pressure in an hour, mm. Hg.
	Sex.	Age.	Eye.	
Ephedrin sulphate 10 per cent . . . . .	F.	49	Left	0.0
	M.	18	Left	+2.5
			Right	+2.0
	M.	14	Left	+0.8
			Right	-1.5
	F.	30	Left	0.0
			Right	-0.7
	M.	34	Left	0.0
			Right	0.0
	M.	37	Left	-2.0
Ephedrin sulphate 10 per cent } Homatropin HBr 0.1 per cent }			Right	0.0
	F.	14	Left	-1.0
			Right	1.2
	M.	16	Right	-4.3
Ephedrin sulphate 10 per cent } Euphthalmin HCl 1 per cent }	M.	18	Right	0.0
	M.	22	Right	+1.0
	F.	60	Right	+2.5
	F.	38	Right	0.0
			Left	+1.5
	M.	24	Right	+1.5
			Left	0.0
	M.	40	Right	0.0
			Left	0.0
	M.	51	Right	+3.5
			Left	+1.2
	M.	21	Right	-2.5
			Left	-1.2
	M.	18	Right	+1.2
			Left	0.0
	M.	22	Left	+3.8
	M.	18	Left	0.0
	M.	16	Left	-1.8

**Intraocular Pressure.** For determining the intraocular pressure during ephedrin mydriasis, a Schiötz tenometer is used. A 2 per cent solution of holocain or a 1 per cent solution of butyn is instilled to anesthetize the cornea. Readings are taken at the time of application of a mydriatic and at the end of one hour when mydriasis is at its height. The results are summarized in the tables above. It will be



seen that the change of intraocular pressure after ephedrin solutions, is small in most cases. The pressure was increased in two instances by 3.5 and 3.8 mm. Hg., respectively, and, in another, it was actually diminished by 4.3 mm. Hg. In 10 other eyes without any mydriatic the intraocular pressure, as measured by the same tenometer, was found to have a maximal variation of  $\pm 3.5$  mm. Hg. in an hour. The changes observed fall, with two exceptions, within the limits of ordinary variations and do not prove that ephedrin raises the intraocular tension.

**Other Effects.** The solutions of ephedrin are but little irritating. Some subjects experienced a burning sensation which lasted for about thirty to sixty seconds. They produce no congestion, or blanching as does an epinephrin solution. They do not cause drying and desquamation of the corneal epithelium as is frequently seen after the use of cocain. There are no ill effects after repeated instillations.

**Comment.** From the foregoing results and from the reports of other clinics, it is clear that ephedrin is a harmless mydriatic in Caucasians. Its action is of short duration and practically does not interfere with accommodation. The light reflex of the pupil is active during ephedrin mydriasis but can be rendered very sluggish by the addition of homatropin or euphthalmin. In nonglaucomatous eyes, it does not raise the intraocular pressure upon application; but in cases of glaucoma it may precipitate acute attacks as in Inouye's<sup>7</sup> case. In glaucoma, however, the use of any mydriatic is a dangerous measure. Cocain<sup>16</sup> and euphthalmin<sup>17,18</sup> have been known to cause the same serious consequences. It is, therefore, always wise in all patients over forty-five years of age, and younger patients having a tendency toward glaucoma, to counteract the action of a mydriatic by the instillation of a miotic. The effect of ephedrin is easily overcome by pilocarpin. Ephedrin is most useful in the examination of the fundus. On a priori grounds it should be also helpful in distinguishing paralytic from spastic miosis although no such report has been made. Since ephedrin produces no cycloplegia, it is useless in refraction.

**Summary.** Ephedrin, especially in combination with homatropin or euphthalmin, is a harmless, convenient, and efficient mydriatic for Caucasians. It has a short duration of action and little influence upon the accommodation. If desired, its effect can be readily counteracted by pilocarpin. It can be used locally in routine ophthalmoscopy for diagnostic purposes. Only in uveitis and iritis does it fail to dilate the pupil.

NOTE.—The authors are indebted to Prof. W. H. Wilmer and his staff of the Wilmer Institute, Johns Hopkins Hospital, for their coöperation in making observations on their patients.

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## NEUROLOGIC ASPECTS OF POLYCYTHEMIA VERA.\*

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THE complaints of patients suffering from polycythemia vera are often referable to the nervous system, but in such a manner that they do not have a localizing value; they often are misleading, or they may be dismissed as functional. In the presence of vascular accidents, which are by no means uncommon in this disease, diagnosis may be difficult. Sometimes the complaints mimic those found in organic syndromes. As a consequence, the disease often presents a confusing clinical picture which may require careful study before a

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conclusion can be made as to its nature. The following case is illustrative:

A clergyman, aged fifty-six years, came to The Mayo Clinic complaining chiefly of dizziness, headache and vomiting. He had been in fairly good health until about two years prior to admission when he had an attack of nausea and vomiting which continued a few days and was diagnosed as gastric neurosis. Since this illness, he had had minor attacks of nausea and vomiting at least once a month until two months prior to admission when the vomiting began to increase gradually until it occurred one or two times a week. About two months after the onset dull frontal headaches appeared three or four times a week, usually more severe in the early morning and in the evening. Occasionally the pain in the head was fairly sharp. The headaches, like the vomiting became increasingly severe in the two months prior to admission. About a year after onset, transient attacks of dizziness began; they became constant in the month prior to admission. The patient described the dizziness by saying "things outside him whirled to the right." Concomitant with the aggravation of nausea, vomiting, headaches and dizziness in the several weeks prior to admission, mild transient numbness in the extremities, a few questionable uncinat seizures, a few transient attacks of diplopia and some blurring of vision, and slight loss of control of the extremities were noted.

On examination, the systolic blood pressure was 158 and the diastolic 124. The blood Wassermann reaction was positive in one test and negative in several subsequent tests. The hemoglobin ranged from 82 to 96 per cent; erythrocytes numbered 5,700,000 to 6,630,000; leukocytes, 7000 to 13,700; the hematocrit reading was plasma 38 per cent, cells 62 per cent, total blood volume, 125 cc. for each kilogram of body weight, and viscosity, 10. Ophthalmoscopic examination of the fundi revealed only slight fullness of the retinal veins. The objective examination of the nervous system was essentially negative. The patient was somewhat disoriented and vague in his statements in a manner suggesting a frontal-lobe syndrome. Venesection was done on several occasions with removal of 400 cc. of blood at each operation without marked relief of symptoms. A diagnosis of polycythemia vera was made and the patient was sent home on expectant treatment.

A further striking example of symptoms simulating those of brain tumor may be cited in Christian's Case IV, in which decompression had been done to relieve the patient of his symptoms due in this case to thrombosis of the cerebral arteries.

The simultaneous occurrence of polycythemia vera with various nervous-disease syndromes either as an essential part of the symptoms or merely in association with the disease has been observed with comparative frequency. In the first case, reported by Vaquez (1892), vertigo and tinnitus were prominent symptoms. The association with migraine is not uncommon.<sup>6</sup> The occurrence of somnolence with polycythemia has been noted,<sup>6</sup> as also various nervous<sup>1</sup> and psychic symptoms, depression, chorea and temporary aphasia.<sup>3,6</sup> Cerebral vascular accidents with accompanying signs and symptoms are comparatively common.<sup>2,5,6,7</sup> Choked disk is not often seen with this disease but does occur.<sup>6</sup> Rare association with disease of the pituitary and pineal glands has also been noted.<sup>4</sup>

The foregoing case is one of 56 cases diagnosed as polycythemia vera in The Mayo Clinic, a study of which has provided the basis of the present discussion. Although the fact is recognized that many of the symptoms and signs of polycythemia vera are not referable to the nervous system yet the high incidence of such neurologic aspects noted heretofore in many cases prompted this analysis to ascertain the relative frequency of symptoms and objective findings

Comparative frequency of neurologic symptoms in polycythemia vera

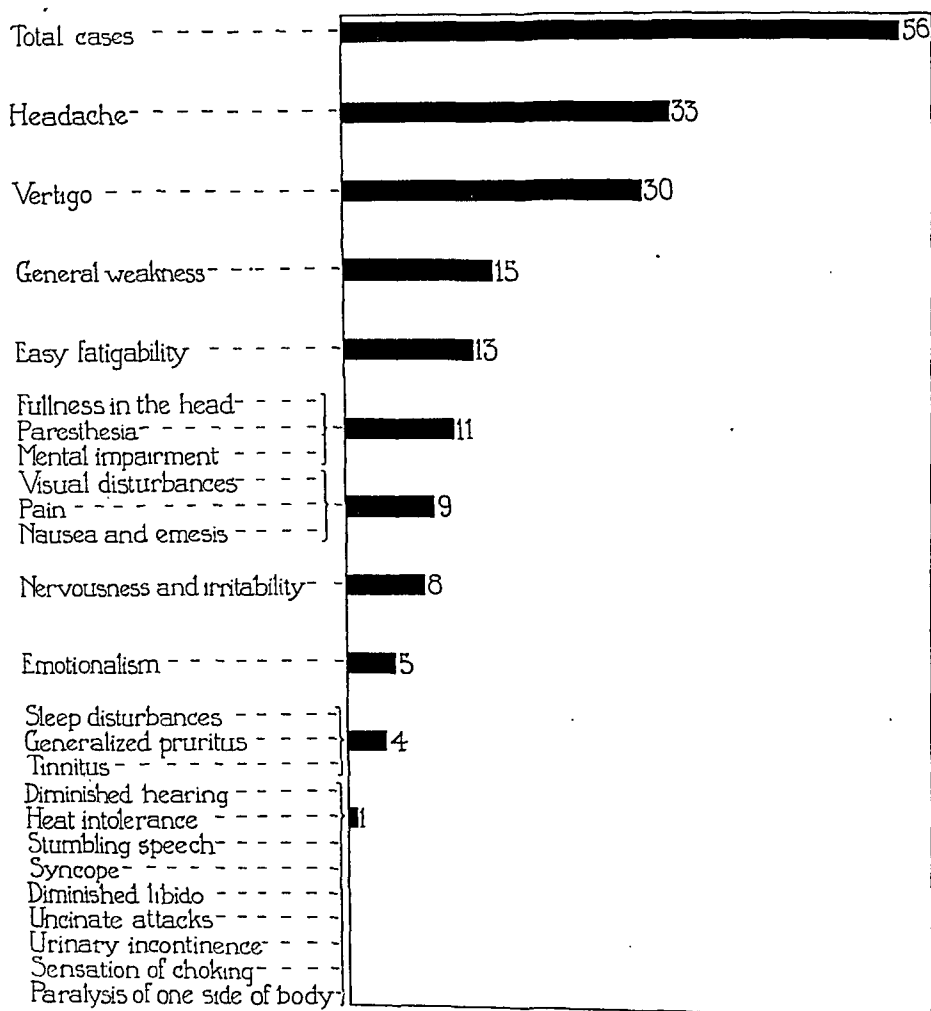


FIG. 1.—Comparative frequency of neurologic symptoms in polycythemia vera.

which may be considered as involving the nervous system. Fig. 1 summarizes the relative frequency of such symptoms.

Headache was the most common neurologic symptom encountered occurring in 33 of the 56 cases. This symptom was neither typical nor constant in type. It was described usually as dull, mild and irregularly recurring without localization. Individually and rarely it was characterized as "bandlike," "single areas of aching about the

head and neck," "expansile," and so forth. In a few cases it was present on the patient's waking in the early morning. In several cases, throbbing and pounding aches and occasional sharp pains were described but could not be distinguished from symptoms of migraine. Migraine was diagnosed in 4 cases in the present series, and it was suspected in several others.

Such headache, as a symptom, is not to be confused in these cases with "fullness in the head" which was noted in 11 cases. However, evidence of increased intracranial pressure was not found objectively in any one of the cases in the series. Characteristic fullness of the retinal veins was noted ophthalmoscopically in the majority of cases but choked disk was not observed.

In point of frequency the second neurologic symptom is vertigo, which occurred in 30 of the 56 cases. This was recorded usually as mild dizziness or so-called locomotor dizziness in which gross coördination is disturbed. The sensation of "heaving ground," or "weakness in the legs," and general discomfort are prominent. The severity of the attack is partly measured by the patient's statement that he "had to sit down" or "hold on to something firm" for a passing moment to avoid falling. The systematized vertigo of organic syndromes was not found except in the case reported.

In 3 cases of the series there were similar atypical attacks in which vertigo was a symptom. The first patient complained of short attacks occurring from one to three times weekly in which a dull headache was associated with moderately severe giddiness, drowsiness and general weakness, and followed by mild confusion and loss of memory. The second patient had attacks once a week to once a month, of sudden and transient dizziness followed by aching throughout the body and general weakness. The third patient "on exposure to cold" had transient attacks of dull headache, moderate dizziness, nausea and general weakness.

The general complaint of "mental impairment" was comparatively common, occurring eleven times. This symptom was usually uncovered incidentally in the course of routine inquiries. It assumed various forms, such as mild transitory confusion at times throughout the day, slight loss of memory, and some slowing up in the speed of thinking. None of these complaints were verified objectively.

Paresthesias were complained of in 11 cases, and were significant only in that they were not constant or uniform, and thus different from paresthesias found in multiple peripheral neuritis and combined degeneration. Complaints such as "burning in the throat," "coldness of one side of the body," "prickly sensations in one hand," and so forth, may be assumed to be entirely functional if one is unaware of the presence of a definite disease syndrome such as polycythemia vera, and may be difficult to interpret in any case.

Nausea and emesis were complained of in 9 cases but could not be traced to any involvement of the nervous system. In 9 other cases

complaints of pain in various parts of the body were likewise recorded. Neither the description nor the cause of the pain is clear in every case. It may be suspected, however, that such a complaint as "aching pains in the arms and legs," pains in various joints, or "tenderness in the muscles" is not to be attributed to any disease of the nervous system.

Besides the more important primary complaints, 8 patients described themselves as "nervous and irritable" in their present illness. This complaint represents undoubtedly one of the milder mental symptoms of which emotionalism, complained of by 5 patients, would seem to be a more advanced degree. This was evidenced by frequent weeping and easily aroused anger.

Nine patients complained of such mild subjective visual disturbances as blurring of vision, and transitory scotoma, the latter being associated with headaches of migraine.

Disturbances of normal sleep were mentioned by 4 patients, 2 complaining of insomnia and 2 of lethargy and drowsiness during the day.

An interesting complication was unaccountable generalized pruritus in 4 cases. In 4 other cases varying tinnitus was likewise complained of but concomitant hearing defects were not present.

Symptoms which were mentioned only once in the series of cases include complaints of diminished hearing, heat intolerance, mild "stumbling" speech, syncope, diminished libido, uncinat attacks, slight urinary incontinence, frequent sensations of choking and paralysis of one side of the body.

The objective neurologic data in polycythemia vera are positive chiefly in cases of vascular accident in which it is presumed thrombosis has taken place in one of the cerebral vessels.

Of the 56 cases here reviewed, a complete neurologic examination was carried out in 12. In 3 of these definite cerebral vascular accidents occurred, in a fourth case there were visual field defects, which were attributed to vascular accident, and in a fifth, in which there was a frontal lobe syndrome in the presence of polycythemia vera, it was suspected that there was a vascular accident, but the patient died without definite clinical evidence, and necropsy was not performed. In the first 4 cases the patient had recovered from the immediate effects of the accident, but had been left with a residuum which in the first 2 cases consisted of partial left homonymous hemianopsia, in the third case partial right hemiplegia, and in the fourth case inferior altitudinal anopsia.

**Case Reports.** The fourth case mentioned was that of a young man, aged twenty years, who came to the clinic complaining of failing vision. Two years prior to admission he had been in an automobile accident in which the side of his head had been struck and badly bruised; the eyelids swelled following this and he could not open his eyes for about two weeks. Within two months following this accident his vision began to fail so that he had

difficulty in recognizing persons at night, and "could not see the flag clearly on the golf course." He apparently had had a slight fainting attack with momentary unconsciousness (vascular accident?) just prior to the onset of the visual failure. The left eye gave him more trouble and as a consequence he consulted an oculist who told him that the right eye was failing also. He was informed at this time that he had atrophy of the left optic nerve and that the right nerve head was choked and showed pallor. The visual fields were approximately the same as they were in the examination at the Clinic. A roentgenogram of the skull showed a small sella turcica and erosion of the posterior clinoid processes. Shortly after this, about five months after the automobile accident, he consulted a prominent neurologic surgeon elsewhere who explored the right occipital lobe expecting to find a tumor because in addition to the ocular findings the ventriculogram showed destruction of the right occipital lobe, but the exploration was negative.

Before operation the patient was aware that he had polycythemia vera and had taken phenylhydrazin hydrochlorid for the condition. About four months after the automobile accident the erythrocytes numbered 6,400,000, and the hemoglobin was 108 per cent. For the last year he had taken phenylhydrazin hydrochlorid; hence the blood picture at the time of examination was altered. During the last six or seven weeks the patient believed the vision in the right eye had been failing more rapidly. He did not have other complaints.

The general examination was essentially negative except for the finding of a slightly enlarged spleen. The blood was normal. The roentgenogram of the skull was negative, showing, however, the trephine area in the right parietooccipital region. Examination of the nervous system showed a slight increase of the deep reflexes on the left side. Examination of the eyes showed, as already mentioned, inferior altitudinal anopsia, and ophthalmoscopic examination of the fundi revealed full pale disks.

The sixth case examined neurologically showed nystagmus, the cause of which was not determined. Examination in the seventh case was negative except for the history and signs which warranted a diagnosis of "simple depression" from the psychiatric point of view.

The eighth case presented evidence of pathologic change of the basal ganglia, the general picture of which resembled Wilson's disease. The polycythemia appeared to be incidental, and the association of the two diseases could not be determined as fundamental. The case was that of a married woman, aged forty years, of relatively low intelligence and correspondingly unreliable history. The chief complaint was stiffness in the movements of the lower extremities and difficulty in walking. The trouble had begun sometime between the ages of twenty and thirty years. She had first noticed clumsiness in some of the finer movements. This had gradually progressed to the present degree of spasticity and incoördination in which the legs were little better than stilts and pes cavus deformity had increased the difficulty in walking. She complained also of dull generalized headaches of four or five years' duration, occasional numbness and dull pains in the feet and legs, mild dizziness with tendency to fall forward or backward, and some emotional instability. The approximate time of the onset of the polycythemia was thus in doubt.

The general examination revealed splenomegaly as well as hepatomegaly of moderate degree. Examination of the blood relative to the polycythemia showed the number of erythrocytes to be 6,090,000, viscosity 6.6, hematocrit reading was plasma 41 per cent, cells 59 per cent and total blood volume 115 cc. for each kilogram of body weight. Serum bilirubin was 2.3 mg. for each 100 cc., but the dye retention test was negative.

The neurologic examination brought forth the presence of rotary nystagmus, dysarthria, slight weakness but increased reflexes and tone in the lower

extremities, questionable bilateral Babinski reflexes, spastic gait, slight irregular tremors, emotional instability, and a general picture which, as mentioned, appeared to resemble Wilson's disease. Neurologic examination in the four remaining cases was essentially negative from this point of view.

In association with polycythemia vera in the present series, neurologic complications other than those already mentioned which may be of interest were: 1 case diagnosed as Raynaud's disease, 1 case of "sphenopalatine neuralgia," or "Sluder's syndrome," 1 case of vasomotor neurosis of the foot with erythromelalgia, and 2 cases diagnosed as neurosis, from the general symptoms.

**Summary.** It thus seems evident that the neurologic aspects of polycythemia vera are extensive and sometimes confusing from the point of view of symptoms. At the same time the disease in itself presents little that is primarily neurologic, objectively, except in respect to vascular accidents which in rare cases may be so involved as to lead to mistaken diagnoses and unnecessary surgical procedures. The diseases associated with polycythemia vera are varied and often include those of neurologic nature.

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## THE SIGNIFICANCE OF HIGH-GRADE ANEMIA IN CHRONIC NEPHRITIS.

WITH A REPORT OF FOUR CASES.

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THE approach to the study of nephritis continues to be that of Bright—an examination of the individual case or group of cases from the clinical and pathologic points of view, a method that is inevitable as long as the etiology of the disease remains obscure.



Although our knowledge of the nephropathies has grown, there are still encountered cases in which the diagnostic features are sufficiently puzzling to warrant comment. In severe cases of chronic glomerular nephritis in particular is this true. In this disease, certain clinical findings have become well recognized as essential factors in reaching the diagnosis. These are arterial hypertension, cardiac hypertrophy, retinal changes and anemia. Exceptions to this clinical picture, however, do occur. Müller<sup>1</sup> and Foster<sup>2</sup> report cases of chronic nephritis in which elevation of the blood pressure or cardiac hypertrophy were not present. Bannick<sup>3</sup> describes 2 cases of severe chronic glomerular nephritis without hypertension, cardiac hypertrophy or retinal changes. Such a marked deviation from the normal cardinal clinical findings makes the diagnosis of the condition a matter of considerable difficulty.

In the present communication a group of cases with severe chronic nephritis is considered in which hypertension, cardiac hypertrophy and retinal changes were either absent or of negligible degree and in which anemia was the chief clinical finding. In each instance, the anemia was so prominent that at first it was considered as the primary disease.

**Characteristics of Anemia.** Anemia in chronic nephritis occurs principally in those cases characterized by nitrogen retention. It parallels the degree of nitrogen retention and is a reliable index of the severity of the condition, assuming, as a result, prognostic importance. It bears no relation to the presence of edema. The anemia is of the secondary type, and leukogenesis is not affected. These facts have been established by various observers, and our findings in this connection are in essential agreement. The average results in a series of cases of chronic nephritis with anemia are summarized in Table I.

TABLE I.—FINDINGS IN CHRONIC NEPHRITIS WITH ANEMIA (51 CASES).

Erythrocytes (average count) . . . . .	2,780,000
Hemoglobin, per cent (average) . . . . .	51
Color index . . . . .	0.9
Urea nitrogen, mg. . . . .	86.3
Creatinin, mg. . . . .	9.3
Edema present . . . . .	18 cases (35 per cent)

The cause of the anemia would seem to be decreased function of the bone marrow, according to Brown and Roth's<sup>4</sup> conclusive study. Neither hemolysis nor hydremia has been demonstrated as a factor in the causation of the anemia. Keith, Rowntree and Geraghty<sup>5</sup> and later Bock<sup>6</sup> found the plasma volume of the blood in severe nephritis remaining constant, variations depending upon the corpuscular content. Aubertin and Yacoel<sup>7</sup> in 2 cases of severe nephritis with anemia found a fatty bone marrow, microscopically showing

no evidence of activity. This depression in the hematopoietic function of the bone marrow is interpreted as an evidence of the toxic process involved in chronic nephritis, and has served to emphasize the widespread character of the extrarenal changes, particularly the extensive vascular injury which would seem to be the chief characteristic of the disease.

The following cases are remarkable in the absence of the usual clinical findings of hypertension, cardiac hypertrophy and retinal changes. They illustrate the parallelism in chronic nephritis between blood-nitrogen retention and marked anemia. With the simple initial clinical finding of anemia, they proved to be severe cases of chronic nephritis as evidenced by the blood-nitrogen findings and the renal-function tests. Primary anemia was ruled out in each instance and a secondary anemia due to any other cause could not be established. It is further to be clearly understood that in no instance were we dealing with acute or subacute nephritis or chronic nephritis with edema.

**Report of Cases.** CASE I.—J. B., a man, aged fifty-two years, farmer, was admitted to the University Hospital, May 24, 1926, complaining of weakness, shortness of breath and palpitation which had been noticeable for about fourteen months, but which had suddenly become worse. There was nocturia once a night. The patient had been rejected for insurance in 1923 because of albuminuria. At the age of sixteen, he had scarlet fever followed by "kidney trouble" for six weeks.

The patient was pale and there was a yellowish tint to the skin, suggesting primary anemia. The heart was not enlarged. The fundi were normal. The blood pressure was 140 systolic and 80 diastolic. The peripheral vessels were not thickened. There was no edema. The spleen was not felt. There were a few small internal hemorrhoids but no frank bleeding. The red blood cells were 2,520,000, and the hemoglobin 32 per cent. The white blood count was 9000, the differential normal. The blood Wassermann reaction was negative. There was free acid in the gastric contents. The urinalysis showed albumin 1, an occasional granular cast and no red blood cells. In the renal function test (Mosenthal modification) the total day urine was 1275 cc., the total night specimen 910 cc. The specific gravity of the two-hour specimens ranged from 1.013 to 1.017. At the time of admission, the blood urea was 77 mg., uric acid 6.4 mg., creatinin 5 mg. for each 100 cc. Later the estimations were urea nitrogen 59.5 mg., uric acid 7.2 mg., creatinin 7.9 mg. The phenolsulphonephthalein output in two hours was 20 per cent. The diagnosis was chronic glomerular nephritis with uremia.

The patient was discharged June 10, 1926. This condition remained unchanged until December, 1926, when he complained of aching and soreness over the body. In February, 1927, he developed a large rectal abscess and died one month later. An autopsy was not obtained.

CASE II.—D. G., a man, aged sixty-seven years, laborer, was admitted to the University Hospital March 15, 1927. He had been well until two weeks prior to admission when he noticed weakness, headache, drowsiness and some nausea with vomiting. A few days before he vomited one-half pint of blood. There had been nocturia three to four times a night for about three months. There was a history of chronic alcoholism.

Physical examination showed a pasty pallor and drowsiness. The heart was not enlarged. The retinal vessels showed early arteriosclerosis. The blood pressure was 140 systolic and 70 diastolic. The peripheral vessels were slightly thickened. Edema was not present. Erythrocytes were 1,900,000; hemoglobin 30 per cent; white blood count 6500, the differential normal. The blood Wassermann reaction was negative. Gastric analysis showed an absence of free acid. Roentgen rays of the gastrointestinal tract were negative. There was a moderate amount of albumin in the urine, many hyaline and granular casts and no red blood cells. Renal function tests showed a fixation of specific gravity and a relative increase in the amount of night urine. The phenolsulphonephthalein output in two hours was 40 per cent. On admission, the blood urea was 59.5 mg., uric acid 7.1 mg., creatinin 2.6 mg. for each 100 cc. After one month's treatment these figures dropped to within normal limits. The patient was discharged April 15, 1927. The clinical diagnosis was chronic glomerular nephritis.

He was seen again in April, 1928, having been well during the interval and doing part-time work. There was still moderate pallor, but no evidence of cardiac hypertrophy or retinal changes. The blood pressure had risen to 172 systolic and 88 diastolic. The urine findings were unchanged. Erythrocytes were 3,540,000 and the hemoglobin 60 per cent. There was no nitrogen retention in the blood.

**CASE III.**—W. C., a man aged thirty-five years, painter, was admitted to the University Hospital, March 30, 1926. He had been well until three weeks before when he noticed weakness, dizziness and on one occasion a small epistaxis. After one week he went to bed, complaining of shortness of breath, nausea and vomiting and pain in the left upper quadrant of the abdomen. Six years previously, he had been refused insurance because of albuminuria.

There was clinical evidence of anemia, marked weakness and dehydration. There were no muscle twitchings. The heart was not enlarged. The fundi were normal. The peripheral vessels were not thickened. The blood pressure was 124 systolic and 70 diastolic. There was no edema. The erythrocyte count was 2,640,000; the hemoglobin 49 per cent. The blood Wassermann reaction was negative. The blood urea was 224 mg., uric acid 6.6 mg., creatinin 26.6 mg. for each 100 cc. The urine showed albumin 2, granular casts and no red blood cells. In the renal function study the total day output was 225 cc. with a specific gravity of 1.006, the night output 275 cc. with the specific gravity 1.010. The phenolsulphonephthalein output in two hours was zero.

After one week, the patient coughed and vomited up small amounts of blood repeatedly. He developed bronchopneumonia and died in a comatose condition twenty-five days after admission. The blood nitrogen remained at about the same level. Ten days before death the plasma CO<sub>2</sub> content was 23 volumes per cent. The highest blood pressure recorded was 130 systolic and 50 diastolic. The clinical diagnosis was chronic glomerular nephritis with uremia.

**Necropsy.** The necropsy observations were as follows: (1) Chronic vascular nephritis; (2) bronchopneumonia; (3) fibrinous pleurisy; (4) hydrothorax, moderate grade; (5) brown atrophy of the liver; (6) remnants of the umbilical stalk.

Each kidney weighed 40 gm. The perirenal fat was adherent and to some extent was replaced by fibrous tissue. The vessels leading to the kidneys were large. The capsule stripped with slight adhesions, and left a reddish rather firmly granular surface almost uniform in character. The cortex measured only 0.3 cm. in thickness. The pyramids were small.

There were petechial hemorrhages into the pelvis which was comparatively large. Microscopically, there was thickening of the vessels with interstitial changes and granular degeneration and necrosis of the tubular epithelium. Some of the glomeruli were contracted and sclerosed and others showed hemorrhagic changes. There were many small areas of lymphocytic infiltration. The heart and vascular system seemed normal. The heart weighed 355 gm.

The bone marrow showed very slight hyperplasia. Many of the cells contained brownish blood pigment.

**CASE IV.**—W. L., a man, aged forty-seven years, farmer; was admitted to the University Hospital, February 8, 1927. His only complaint was nocturia of one year's duration. Otherwise he had been perfectly well. The past history was not remarkable.

The patient appeared anemic. There were no retinal changes. The left cardiac border was just outside the mid-clavicular line. The peripheral vessels were not thickened. The blood pressure was 145 systolic and 60 diastolic. Edema was not present. The erythrocyte count was 2,070,000; the hemoglobin 44 per cent; the leukocytes 9050 with normal differential. The urine showed some albumin, a few granular casts and no red blood cells. The blood urea was 73.5 mg., the uric acid 7.7 mg., and the creatinin 8.8 mg. for each 100 cc. Renal function showed absolute fixation of the specific gravity to the level 1.011. The phenolsulphonaphthalein return in two hours was 12 per cent. The blood Wassermann reaction was negative.

The patient was in the hospital for sixteen days and was allowed to return home to attend to some business. He returned in six weeks' time with a large carbuncle over the right side of the face, and died one week later.

**Necropsy.** The postmortem observations were as follows: (1) Chronic progressive vascular nephritis; (2) lobar pneumonia, right; (3) acute pericarditis; (4) slight hypertrophy of the heart; (5) adhesive pleuritis; (6) cystitis; (7) excision of the skin and subcutaneous tissues of right temporal region; (8) septicemia (*Staphylococcus aureus*).

The right kidney weighed 80 gm., the left 70 gm. The capsule in each case stripped fairly readily, leaving a moderately roughened granular surface. The kidneys were pale in color. The cortices averaged 5 mm. The normal markings were distorted and made out with difficulty. The pelves were large and contained considerable fat. Microscopically the walls of both the large and small arterioles were thickened. Most of the glomeruli showed changes. Some were completely hyalinized, in others the capsule was thickened and contracted. There was extensive infiltration of the interstitial tissue with mononuclear cells and polymorphonuclears. There was cloudy swelling of the tubules.

The findings in the 4 cases are summarized in Table II.

**Comment.** The only clinical manifestation of severe chronic nephritis may be anemia. The diagnosis in such cases is made evident by the finding of retention of the blood-nitrogen constituents. In certain cases, as in Case II above, the degree of the anemia may be increased by frank hemorrhages, so often seen in the course of various types of nephritis. In the absence of associated clinical data giving a clue to the severity of the process and particularly to the prognosis, it seems evident that anemia alone must be regarded

TABLE II.—A SUMMARY OF THE FINDINGS IN FOUR CASES OF CHRONIC NEPHRITIS WITH ANEMIA.

	Physical signs.				Blood.		Urine.			Blood nitrogen.		Phenolsulphonethalein output 2 hrs. (per cent).	Renal function.	Comment.
	Hyper-tension.	Cardiac hypertrophy.	Edema.	Retinal changes.	Erythrocytes in millions.	Hemoglobin, per cent.	Albumin (grade).	Casts (grade).	Erythrocytes (grade).	Urea, mg.	Creatinin, mg.			
Case 1	0	0	0	0	2.52	32	1	1	0	77.0	5.0	20	1.013 to 1.017	Died nine months later with large renal abscess.
Case 2	0	0	0	early sclerosis	1.90	30	1	1	0	59.5	2.6	40	1.010 to 1.011	Living and at work one year later.
Case 3	0	0	0	0	2.64	49	2	1	0	224.0	26.6	0	1.006	Died twenty-five days after admission.
Case 4	0	Slight	0	0	2.07	44	1	1	0	73.5	8.8	12	1.011	Died two months later with local infection and septicemia.

as evidence of renal insufficiency. The practical importance of this fact is best illustrated in cases of hypertension and arteriosclerosis in which, as Adams and Brown<sup>8</sup> have pointed out, the presence of anemia (ruling out complicating disease) should be considered as evidence of kidney damage with existing or preëxisting renal insufficiency. Thus anemia serves as an important differentiating point between chronic glomerular nephritis on the one hand and the clinical entity "malignant hypertension" or the severe hyperpiesia of Allbutt on the other, comprising in these latter terms cases of widespread vascular disease which do not show distinct renal damage. The peculiar association between anemia and the nephritic factor in severe cardiovascular disease is thus manifest.

Three of the cases reported died within a year from the time of being seen. This fact again serves to emphasize the importance of anemia as a prognostic sign of ominous degree. As shown by Brown<sup>9</sup> and other observers, the presence of a severe anemia in chronic glomerular nephritis has practically the same serious prognostic significance as blood creatinin values of 5 mg. per 100 cc. or over, indicating a fatal termination within a two- and one-half year period at least. Therefore, just as anemia stands in close association with actual damage in the renal tissues, its presence in a chronic form and even in a moderately severe degree indicates renal injury to the point of serious insufficiency beyond hope of repair.

In this generalization one must be careful to distinguish those cases of chronic glomerular nephritis of the so-called hemorrhagic type. In such instances the anemia may be an expression of a recent period of hematuria, accompanying what is apparently a phase of acute toxic injury. This phase subsequently subsides and renal function is reëstablished to the point of adequate maintenance. We have under our care at the present time a patient of this type, who was first seen nine years ago at which time there was a marked reduction in renal efficiency as evidenced by fixation of the specific gravity and retention of the blood-nitrogen constituents. There was constant hematuria and an erythrocyte count below three million. Red blood cells continued to appear in the urine for at least two years and then ceased. The erythrocyte count rose and the renal function improved. At the present time the patient is doing full-time work. There is still evidence of chronic nephritis of moderately severe grade but the red blood count is now within normal limits. The anemia in such instances must be interpreted as a result of the hemorrhagic diathesis and not as an evidence of profound toxic injury to the renal tissues and bone marrow.

A striking feature of the cases reported is the fact that the patients, previously in reasonably good health rather suddenly became ill and at the time of the first visit to the hospital were found to have renal changes of severe degree. The nephritic process had pro-

gressed silently to a point where uremia developed and a complete breakdown of renal function was imminent. The progress downward from that point was rapid. This again emphasizes a feature characteristic of chronic glomerular nephritis, the insidious progress of the disease to the point of gross renal insufficiency.

In the one case in which the bone marrow was examined, it was found to consist for the most part of fatty tissue. The cellular elements were slightly increased in amount. Brownish blood pigment was noted in many of the cells. The evidence of hyperplasia appeared to be rather below that seen in a secondary anemia of similar degree associated with some other cause. However, the pathologic picture was not definite enough to suggest decreased blood formation.

It has been assumed, as already noted, that the anemia of chronic nephritis is the result of inadequate hematopoiesis due to a toxic agent incidental to the nephritis. The pathologic observations of the bone marrow which have been made fail to give convincing support to this hypothesis. It has been our experience that the bone marrow in such cases corresponds to that found in the simple chronic anemia associated with malignant disease or long-continued sepsis. Hypoplastic characteristics have not been noted. This is a general observation and is not based on intensive study of the bone marrow in these cases. It is probable that injury to the bone marrow does occur, but careful study of the hematopoietic organs must be made before this conception can be fully accepted.

**Summary.** Four cases of severe chronic glomerular nephritis with uremia are reported, in which hypertension, cardiac hypertrophy and retinal changes did not occur and in which anemia was the single cardinal clinical finding.

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## SICKLE-CELL ANEMIA WITH CASE REPORT OF SPLENECTOMY.

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SPLENECTOMY in the treatment of sickle-cell anemia has been reported by Hahn and Gillespie,<sup>1</sup> and Stewart,<sup>2</sup> and by Bell, Kotte, Mitchell, Cooley and Lee.<sup>3</sup> To these reports we are able to add another, the seventh splenectomy for that condition to be found in the literature, if the case of Giddings cited by Bell and others is included.

**Case Report.** E. F. colored, male, aged four years, was admitted to the Children's Ward of the Roosevelt Hospital on July 15, 1927, the chief complaints being headache, fever and vomiting of five days' duration. For the past year the child had been subject to intermittent attacks of headache, fever, drowsiness, vomiting after meals and generalized abdominal pains. These attacks usually lasted from one to three days and occurred at intervals of from one to three months. In the interim, the child was apparently in normal health. The present attack had lasted twelve days and was more severe than on any previous occasion.

He had been observed at the Vanderbilt Clinic since shortly after birth. Delivery had been normal, the birth weight being 9½ pounds. He was breast fed for nine months and developed normally. At the age of two, he was examined at the New York Nursery and Child's Hospital, where it was found that he was malnourished, and had a large hard spleen and general glandular enlargement. The Wassermann reaction was negative. The blood showed 3,600,000 red cells and 12,500 white blood cells.

Examination on admission revealed a poorly-nourished negro boy. The scleræ were clear, mucous membranes markedly pale, the tonsils large but not diseased. There was a loud blowing systolic murmur heard over the entire precordium, loudest in the pulmonic area; probably hemic. Examination of the abdomen revealed left upper quadrant tenderness without rigidity and a greatly enlarged spleen, the edge being palpable below the umbilicus, hard and smooth. The liver was slightly enlarged. A few shotty lymph nodes were felt in the submaxillary group.

Routine urine and stool examinations were all negative. Shick and tuberculin and Wassermann examinations were all negative. The blood showed: Hemoglobin, 12 per cent (Sahli); red blood cells, 950,000; white blood cells, 12,500; with 45 per cent polymorphonuclears, 20 per cent small and 30 per cent large lymphocytes. The red cells showed central pallor and there was considerable anisocytosis and poikilocytosis. No sickle cells were reported at this time, and the condition was not suspected.

A provisional diagnosis of von Jaksch's anemia was made, Gaucher's disease also being considered.



The day following admission the child developed a bronchopneumonia and was very sick. A transfusion was resorted to three days later, 100 cc. of whole blood being given without reaction. There followed a marked symptomatic improvement, the child being able to sit up in bed, although still remaining quite apathetic. There was considerable improvement in the blood picture (see table). He continued to run a low-grade fever which varied between 99° and 101° F., with frequent remissions to the normal. At the end of five months in the hospital, little change for the better could be observed over his condition shortly subsequent to the transfusion. His spleen had reached the crest of the ilium, was very hard and smooth and not tender. It was felt, however, that the child was entitled to a splenectomy as a last resort, because of the increasing size of the spleen and the absence of clinical improvement under symptomatic treatment, and on December 12 this was done by Dr. James Russell, the operation being preceded by two transfusions of 130 and 240 cc. respectively.

The spleen was removed with considerable difficulty because of its large size, but the postoperative course was remarkably smooth. The child was up and about in two weeks and showed continued improvement both clinically and hematologically. Eleven days postoperative the fragility test showed that hemolysis began at 0.42 and was complete at 0.26. This determination had not been made preoperatively. The blood picture may be followed in the accompanying chart.

The spleen measured roughly 18 by 12 by 9 cm. and weighed 621 gm. The consistency somewhat resembled that of the liver. The cut surface was a dark purplish red with scattered white spots. The microscopic picture was one of great congestion and considerable fibrosis. The pulp appeared normal. The hospital pathologic diagnosis was chronic congestion of the spleen and interstitial splenitis. The slides were submitted to an eminent pathologist who reported a chronic interstitial splenitis with universal capillary varices and focal proliferation of the pulp endothelium. Up to this time, no suspicion of sickle-cell anemia had existed. The diagnosis was finally made by Dr. Martha Wollstein, pathologist to the Babies Hospital. She reported finding sickle-shaped red cells in the sections of the spleen. Moist smears of the blood then showed typical sickle cells. They were not numerous, about two or three to each high-power field, and showed only slight increase in number after standing for two days. Fresh smears examined in a chamber saturated with carbon dioxid, according to the method and apparatus devised by Hahn, showed numerous sickle cells, many of which assumed normal shape when oxygen was admitted to the chamber. Examinations made over a period of fourteen months showed a persistence of the sickle-cell trait.

Fresh blood smears of two brothers and one sister and of both parents failed to reveal sickle cells.

At the time of discharge, three and one-half months after splenectomy, the child was in excellent condition.

**Subsequent Course.** He was readmitted one month later in about the same condition for further observation. At this time the hemoglobin was 61 per cent, red blood cells, 3,300,000. He was subsequently discharged (six weeks later) with very little change observed. Blood count at the time of discharge was hemoglobin, 55 per cent and red blood cells, 3,000,000. Fresh smears showed many sickled red cells.

He was again admitted September 4, 1928, nine months after splenectomy, with an interval history of continuous fever and irregular attacks of abdominal pain. Just prior to the present admission he had complained of some pain in his ankles and his mother thought he had run some fever for five days. He was, however, in comparatively good health. He was undernourished but lively and apparently comfortable. His liver was moderately

enlarged, and there were no other physical findings of note. The hemoglobin was 58 per cent; red blood cells, 3,800,000; white blood cells, 15,000; polymorphonuclears, 45 per cent. Fresh smears showed sickle cells and a fresh hanging drop examined in the closed chamber saturated with carbon dioxide revealed a large percentage of sickle forms. Resistance was greatly increased, hemolysis beginning at 0.34 and complete at 0.22. The icteric index was 5; the direct van den Bergh reaction, negative, the indirect showed 1.2 mg. bilirubin per liter.

## BLOOD COUNTS.

Date.	Hgb., per cent.	R. B. C. in mil- lions per c.mm.	W. B. C. in thous- ands per c.mm.	Polys.	Lym.	Spreads.
7/16/27	12	0.95	12.5	45	..	Small lymphocytes, 20 per cent. Large lymphocytes, 30 per cent.
7/19/27	Transfusion 100 cc.					
7/23/27	26	1.6	43.0	22		
7/25/27	..	..	19.4	21	..	Small lymphocytes, 36 per cent. Large lymphocytes, 31 per cent.
8/ 1/27	45	2.8				
8/ 8/27	35	2.7				
8/16/27	50	2.4				Normoblasts and megaloblasts 37 per 100 white blood cells.
8/29/27	35	1.4	12.6	23		
9/19/27	25	2.5	11.4	40	57	
9/30/27	40	2.5	6.0	52		Red blood cells showed anisocy- tosis, central pallor, no nu- cleated red blood cells, no ab- normal white blood cells.
10/ 4/27	36					
10/17/27	41	2.7	16.0	69	..	
10/31/27	47	2.9	10.1	72		
11/18/27	..	..	20.4	72		
11/23/27	39	2.1				
12/ 7/27	(Transfusion 130 cc.)					
12/ 9/27	44	3.6				
12/11/27	(Transfusion 240 cc.)					
12/12/27	Splenectomy					
12/22/27	38	3.5				
12/25/27	32	3.8				
12/30/27	48	3.4				
1/ 8/28	55	3.6				
1/22/28	50	3.0				
2/13/28	40	2.9				
2/22/28	55	4.0				
3/15/28	..	..	18.8	74		
4/27/28	61	3.3				Many sickle forms. Many sickle forms.
6/18/28	55	3.0	..	..	..	
9/ 5/28	58	3.8	15.2	45	..	
2/ 1/29	50	3.6				

## WEIGHT.

Date.	Pounds.	Ounces.	Date.	Pounds.	Ounces.
7/30/27	26	5	2/25/28	35	3
8/16/27	35	..	3/ 3/28	35	5
11/15/27	34	2	3/10/28	35	9
12/12/27	Splenectomy		3/17/28	35	14
12/31/27	33	15	4/28/28	35	
1/28/28	35	..	5/25/28	36	
2/18/28	35	4			

**Comment.** Sickle-cell anemia has been studied by Herrick,<sup>4</sup> Sydenstricker,<sup>6,7</sup> Huck,<sup>8</sup> Graham<sup>9</sup> and others. It is apparently a familial disease transmitted according to the Mendelian law, appearing as a dominant factor. Up to the present, all the cases reported have been in those of negroid blood. Cooley and Lee in an examination of 100 negro dispensary patients found that approximately 7 per cent showed the sickle-cell trait. Of this relatively large percentage only a very small portion apparently developed sickle-cell anemia. The causative factors in the production of the anemia are not known. Sydenstricker states that there are two stages in which the condition manifests itself, one latent and one active. The most characteristic symptoms are severe anemia, joint and muscular pain, recurring attacks of abdominal pain and low-grade fever. One of the frequent findings is leg ulcers. In the latent stage according to Sydenstricker, "patients displaying no symptoms of anemia will unquestionably give a history of rheumatic attacks, pain in the epigastrium and left hypochondrium, and attacks of weakness and dyspnea, which have been separated by periods of normal health."

Hahn and Gillespie object to the use of the term, "latent sickle-cell anemia" as applied to clinically-well individuals who are not anemic, and prefer to view the sickle-cell trait as an hereditary characteristic, predisposing those affected by it to hemolytic anemia. They also believe that anoxemia by inducing and increasing sickle-cell formation may be an important factor in producing increased hemolysis (that is, the so-called active stage as differentiated from the latent stage) and they point to the prevalence of cardiac and pulmonary complications in the active cases reported.

The greatly increased urobilin excretion in the stools and urine and the presence of abnormal amounts of bilirubin in the blood (van den Bergh reaction) are definite indications of an excessive hemolysis. This fact and the reticulosis (increased reticulocyte count) point to a similarity between this condition and hemolytic icterus. An unanswerable objection however, to identifying sickle-cell anemia with hemolytic icterus is the normal or increased resistance to salt solution as compared with the classic increase in fragility in the hemolytic icterus group.

Chief interest centers around the blood. In the active stage there is constantly a low hemoglobin, ranging from 10 to 40 per cent, with red-cell counts between 500,000 and 4,000,000. The color index averages about 1, sometimes a little higher. Platelets are normal or slightly increased. A fresh blood smear in an active case will usually show a few sickle cells, which increase in number from three to six hours, and reach their maximum in twenty-four hours. In a moist preparation the cells return to normal in three to nine days. That the return to normal is not due to a lacking of the sickle cells, thus revealing the obscured normal cells has been demonstrated by the work of Bell<sup>3</sup> and others who took serial

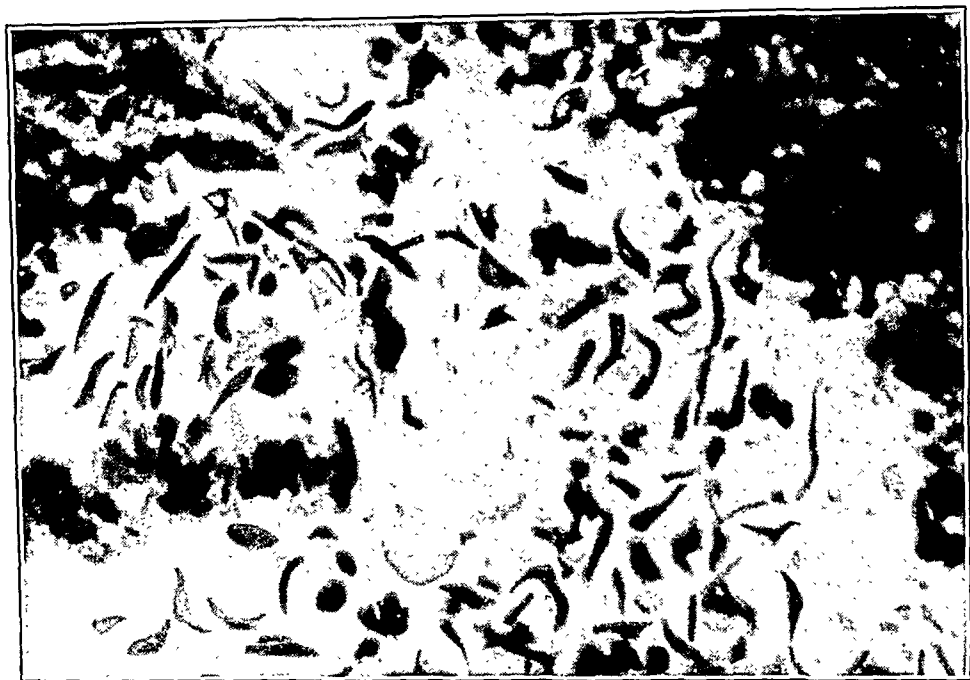


FIG. 1.—Section of spleen showing sinus containing many sickle cells.



FIG. 2.—Blood smear showing typical but not extreme sickling.



photomicrographs at two-day intervals of the same field and observed the successive changes of the same cells from sickling to a normal state.

That the peculiar elongated appearance of the cells is not due to a mechanical factor is shown by the work of Hahn, who by the apparatus mentioned above, demonstrated that the cells suspended in a medium of appropriate hydrogen-ion concentration in a closed space, returned to normal only on the admission of oxygen to the chamber and could be made to assume their characteristic sickle shape again upon the withdrawal of oxygen.

The blood smear also shows the usual changes of a secondary anemia, anisocytosis, poikilocytosis, polychromatophilia. Nucleated red cells are seen in addition. Reticulocytes are markedly increased in number, and apparently this increase is in direct relationship to the decreased fragility, the reticulocytes always being among the nonhemolyzed. There is no connection between the amount of sickling and the degree of anemia. There is marked leukocytosis running as high as 54,000. Myelocytes are frequently seen.

Splenectomy for sickle-cell anemias was first suggested by Sydenstricker and Huck. The first case of splenectomy for this condition was reported by Hahn and Gillespie<sup>1</sup> in February, 1927. Since then, four more complete case reports have appeared. In Hahn and Gillespie's case the patient was moderately improved, both clinically and hematologically four months after splenectomy. Hemoglobin and red-cell counts increased rapidly, and as is usual after splenectomy,<sup>10</sup> there was a corresponding decrease in hemolysis.

The second case, reported by Stewart,<sup>2</sup> was unusual in that it occurred in a child of apparently white ancestry although the maternal grandmother was of Cuban descent and had that source as a potential admixture of negroid blood. The spleen which was removed was small, and had gone through a stage of hypertrophy to a stage of atrophy. The case had been observed for five years, and the spleen previously reported as extending 6 cm. below the costal margin when the child was two and one-half years of age, had apparently atrophied so that at the age of four years it was not palpable. The next year, at the age of five, splenectomy was done a few months after sickling had been observed for the first time. This case showed little improvement, the general condition at the end of two months being about the same as before splenectomy.

The third case, that of Bell<sup>3</sup> and others, was temporarily benefited, but six months after operation, severe anemia was again observed.

In the fourth case, that of Cooley and Lee,<sup>3</sup> there was much less improvement in the blood picture, but marked symptomatic improvement at the end of six months. This case was complicated by two severe attacks of lobar pneumonia.

The fifth reported case, that of Hahn,<sup>5</sup> showed remarkable clinical improvement, five months after splenectomy. Incidentally, this

case showed an unusual variation in the leukocyte count, which ranged from 43,000 to 6600.

In no instance was the sickle-cell trait abolished by splenectomy.

The spleens varied in size from 46 gm. (Stewart's case) to 621 gm. (case described by us). The pathologic picture in the majority of cases was essentially the same—enormous congestion, considerable fibrosis, and in Bell's case, an enormous increase in the reticulum fiber. (Foot's modification of Bielschowsky-Maresch-Gieson stain.)

The rôle played by the spleen in this disease is obscure. No such marked and permanent effects are obtained by splenectomy here as in the hemolytic jaundice group. Hahn and Gillespie do not believe that the sickling is due to the influence of the spleen, but that this organ plays an important part in causing hemolysis of the damaged sickle cells, and that because of its overfunction it passes from the stage of congestion to fibrosis and atrophy. Only 15 per cent of the cases give evidence of an enlarged spleen clinically.

It is unfortunate that the tardy diagnosis in our case renders hematologic data incomplete. We have been able to follow a case for a longer period of time than any one previously reported. Another feature is the enormous size of the spleen. It is interesting to conjecture whether the improvement after operation is somewhat related to the size of the spleen, the least progress being in cases where the spleen is atrophic, the greater progress in cases such as the one herein reported, in which the spleen is greatly enlarged. Possibly splenectomy allows the blood mechanism to regain in a measure its lost equilibrium, lessened hemolysis being a factor. The same relatively greater improvement after removal of a large spleen than of a small spleen has been noted in pernicious anemia (Pearce, Krumbhaar and Frazier<sup>10</sup>).

**Summary.** 1. The seventh case of splenectomy for sickle-cell anemia is presented.

2. The extreme size of the spleen is a noteworthy feature.

3. The clinical condition fourteen months after splenectomy is described as greatly improved.

4. A brief review of the splenectomized cases is presented, attention being drawn to the fact that in no case has the sickle-cell trait been abolished by splenectomy.

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## BRAIN TUMORS IN CHILDHOOD.\*

## A CLINICOPATHOLOGIC STUDY.

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It is the general opinion of the lay public, and to a lesser degree of the medical practitioner, that cerebral new growths are nonexistent or are of extremely rare occurrence in infancy and childhood. During the past twenty years it has become progressively more evident that such growths are not a rarity but that they are in fact of relatively common occurrence in neuro-pediatric practice. Those who are aware of their occurrence are also frequently of the opinion that they are, in the majority of cases, absolutely malignant and inoperable, but with the advance of special surgical technique the proportion of successes in these life-saving operations is increasing very rapidly. At the present time, this type of neurosurgery has a relatively high mortality but the death incidence is dropping year by year, and without surgical intervention death is inevitable. In many cases a suboccipital decompression and deep therapy radiation obtain relief from headache, blindness and mental derangement which are the usual accompaniments of these growths.

**The Frequency of Juvenile Tumors.** In consideration of the aforementioned premise I have investigated the prevalence of juvenile brain tumors in the clinics of some of the hospitals of Philadelphia. Among 350 case records of verified brain tumors examined on the services of the Philadelphia, Children's, University, Episcopal and Orthopædic Hospitals, I discovered 23 cases in children and of these 23, 15 were cerebellar gliomata. It was interesting to note that 12 of these cerebellar growths were in female children and but 3 were in males. There were 3 cerebral gliomas, 1 cerebellopontile angle cyst, 1 pineal gland spongioblastoma, 1 metastatic sarcoma from a primary orbital melanotic sarcoma, 1 pontile glioma, 1 suprasellar cystic adenoma and 2 tuberculomas: 1 of the cerebellum, the other of the cerebellopontile angle.

The diagnosis of a cerebral new growth in a child is more difficult than in an adult but the localization of these lesions in children may be determined by a careful neurologic examination. The proportion of juvenile to adult cases in my series is about 1 to 14. Dr. Harvey Cushing<sup>1</sup> reports that out of 1108 verified brain tumors, only 154 were diagnosed in preadolescence; his opinion concerning this small proportion being that many more tumors go unrecognized

\* Read before the combined meeting of the Philadelphia Pediatric Society and the Philadelphia County Medical Society, Wednesday Evening, May 9, 1928.



in children than in adults and the ratio in his much larger series of cases is approximately 1 to 7. His statistics were taken from a specialized neurosurgical service where brain tumor consciousness is much more alert than in a generalized hospital service. With this fact in mind, I believe that with more careful observation a greater proportion of these cases can be diagnosed prior to autopsy. From a review of this vast number of cases, Dr. Cushing reports that the types of tumor seen in children differ from those occurring in adult life. In his total of 154, there were 116 gliomas and 21 congenital tumors. There were only 6 tuberculomas and but 2 pituitary adenomas. His findings were also of interest in that in children the predominating site for tumor formation was in the cerebellum; 85 of the total of 154 being in the cerebellum and but 44 in the cerebrum. His proportion of cerebellar growths is essentially the same as noted in my much smaller series.

**General Symptomatology.** In my entire series of new growths in children a somewhat similar general symptomatology was noted: a history of a rather rapid onset in which the child became suddenly ill with vomiting and headache, which was soon followed by drowsiness and signs of increasing intracranial pressure as noted by a rapidly developing choked disk with retinal hemorrhages, disturbance of gait, and enlargement of the head and MacEwan's "cracked-pot" sign in infantile cases, plus the localizing symptoms of the growth which may be determined by careful neurologic examination.

**Types of New Growths.** 1. *Tuberculomas.* It is of interest to note that there were but two tuberculomas in my series and several writers have recently reported a lessening proportion of tuberculous brain lesions, especially tuberculomas. In 1888, Dr. M. Allen Starr<sup>2</sup> reported that 50 per cent of his series of more than 300 brain-tumor cases were tuberculomas. Dr. Cushing, however, found that but 3 per cent of his cases were caused by the tubercle bacillus. This ratio reduction is of particular interest as being significant of the inroads which medical science is making into the prevalence of tuberculosis in general. In 1888, the deaths from tuberculosis were greater than those from any other disease, but as a result of the campaign of education that has been waged against tuberculosis in this country the death rate has become so reduced that tuberculosis now occupies fifth place in the mortality list. It is estimated that general tuberculosis is only one-half as prevalent as it was at that time, and it is now being recognized in its incipiency, and rational methods of treatment are being instituted much earlier, thus preventing the secondary complications such as tuberculomas which were so common when Dr. Starr reported his series in 1888. Tooth<sup>3</sup> reported, in 1912, on a series of 500 intracranial tumors from the records of the National Hospital in London, among which there were 14 tuberculomas occurring in the ratio of 2.8 per cent. Clark,<sup>4</sup> in 1916, reported 6 per cent of tuberculomas among a series of 100 cases

examined on the service of Dr. Spiller at the Hospital of the University of Pennsylvania. Several other writers of recent date have reported tuberculomas in ratio from 2 to 6 per cent, and in the series of some 350 cases that I examined I have been able to discover but two verified tuberculomas. Many of these growths appear to be operable but Van Waganan<sup>5</sup> reports that while everyone of a series of 6 cases operated upon for the removal of a tuberculoma survived operation very well, they all died of an acute tuberculous meningitis or tuberculosis within four to eight weeks after the operation. Three of these were in children and they had cerebellar tuberculomas. The usual result after operation is a rapid termination of life through the medium of generalized tuberculosis, especially of the meninges. There is an occasional instance in the literature of operation for tuberculoma with recovery. Dr. Charles Frazier<sup>6</sup> reports a case of this type with operation and survival for eight years following. Elsberg also reports a patient as living for two and a half years after an incomplete removal of a cerebellar tuberculoma. The reason for operating on tuberculous growths is a palliative one to afford relief from the excruciating headache and increasing blindness and other pressure symptoms, rather than as an absolute curative procedure. It is the opinion among neurosurgeons at this time that it is better not to tamper with these tuberculous growths other than to give them room by palliative decompression.

2. *Congenital Tumors.* The usual types of new growths that we see in children are the congenital tumors and the gliomas. The former are generally suprasellar lesions arising from an anlage of Rathke's pouch and these tend to become calcified cysts and interfere with the functions of the pituitary body, thus producing symptoms of dyspituitarism. These pituitary adenomas are usually hypophyseal in origin. At their onset they are accompanied by headache, but this is not a constant symptom. Cushing<sup>7</sup> reports that he has operated upon 605 cases with this diagnosis, 149 by the transsphenoidal and 19 by the transfrontal route with a mortality of 9 with the transsphenoidal and of 5 by the transfrontal route.

The meningiomas, acoustic tumors and endotheliomas, so common in adult life, are quite uncommon in childhood.

3. *The Glioma Group.* The glioma group preponderate in childhood, both as regards number and malignancy. They are the pre-adolescent tumor and Cushing states that they constitute about 75 per cent of the new growths in preadolescent brains, and 40 per cent of all brain tumors. Bailey<sup>8</sup> classifies gliomas into 14 types, but primarily as spongioblastomas, medulloblastomas and astrocytomas, and of these the medulloblastomas are the frequent tumors of childhood.

A. *Medulloblastomas.* Medulloblastomas usually occur in the midcerebellar region, arising from the roof of the fourth ventricle, and project into the vermis. This situation places them in the most

critical position to endanger life and to produce an early internal hydrocephalus by pressure on the *iter*. The cells comprising these tumors are of ectodermal origin and are potential gliocytes rather than neurocytes; they are of the undifferentiated type and somewhat resemble the round-cell sarcoma. Symptomatically, these tumors, because of their location close to the *iter*, tend to produce an internal hydrocephalus and therefore the symptoms occurring are rather abrupt in onset and are essentially headache, vomiting, rapidly increasing choked disk and unsteadiness of gait. In those children whose cranial bones have not united there develops a rather rapid separation of the cranial sutures and an obvious increase in the size of the head and the characteristic "cracked-pot" sign in the skull on percussion. Ataxia and incoördination become progressively more apparent as time goes on and in their later stages, the typical cerebellar fit with retraction of the head, respiratory difficulty and symptoms of meningitis occur. Drowsiness increasing to stupor is a relatively late symptom and when it occurs, death is near.

At autopsy and at operation, medulloblastomas appear to be fairly circumscribed and apparently possible of enucleation, but histologic examination of the surrounding tissues generally shows invasion of them by the tumor cells, which would cause a recurrence of the growth even after careful enucleation. These tumors tend to force their way down through the foramen magnum and therefore are in a situation to cause the patient's death if lumbar puncture is attempted. When these tumors are examined microscopically they are composed of rounded sarcoma-like cells with big oval nuclei, appearing generally as a structureless mass or they may lie in a connective-tissue stroma like a true sarcoma.

*B. Astrocytomas.* The astrocytomas are also a frequent tumor in childhood and their commonest site is also in the midcerebellar region. Cushing states as a result of his great number of cases in children that there is "A two to one chance of finding, usually in the midcerebellar region of children, a surgically favorable glioma." There is almost a pathognomonic symptom complex with this type of tumor consisting of rapid onset of symptoms, headache, vomiting, failure of vision, awkwardness in locomotion, stupor, choked disk and frequently enlargement of the head. Children are not as prone as adults to complain of a beginning deficiency in vision and for this reason the eyegrounds are apt to be neglected and an existing choked disk will not be determined if the ophthalmoscope is not used. Experience has shown that it is practically impossible to enucleate these growths in their entirety, but without surgical intervention death, from the internal hydrocephalus and with great suffering, is inevitable and fairly quick. A simple suboccipital decompression followed by persistent deep Roentgen ray therapy has proven to be the technique of choice in dealing with these lesions, as it relieves the painful pressure symptoms, saves what vision remains and prolongs life comfortably for a period up to about two years.

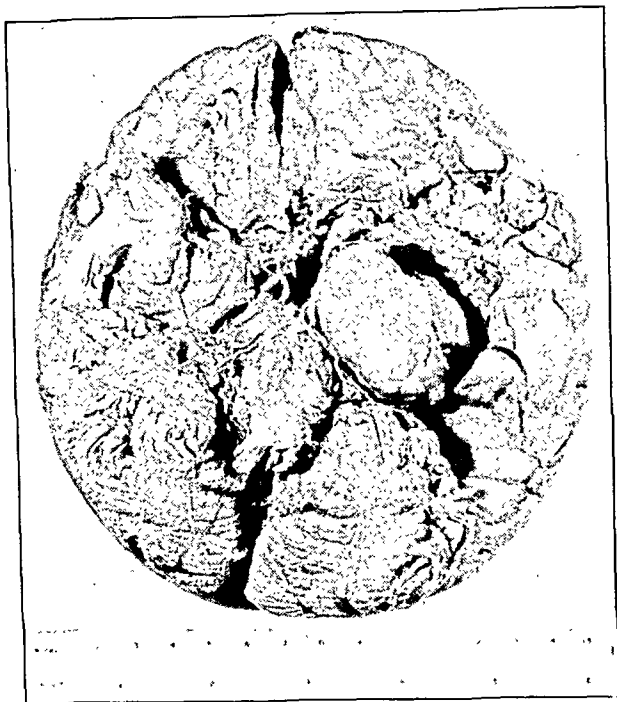


FIG. 1.—Tuberculoma of the Right Cerebellopontine Angle. This boy, from the service of the Children's Hospital, had been admitted to the Hospital in 1919, when eight years of age, suffering with a tuberculous pericarditis. His father was suffering from advanced pulmonary tuberculosis at the time. In December, 1920, he was readmitted suffering with headache, fever, drowsiness and vomiting and he was found to have a high degree of choked disk. At autopsy a generalized tuberculous meningitis was discovered with the large tuberculoma noted in the photograph. Acid-fast bacilli and typical tuberculous structure were discovered in this growth on microscopic examination.

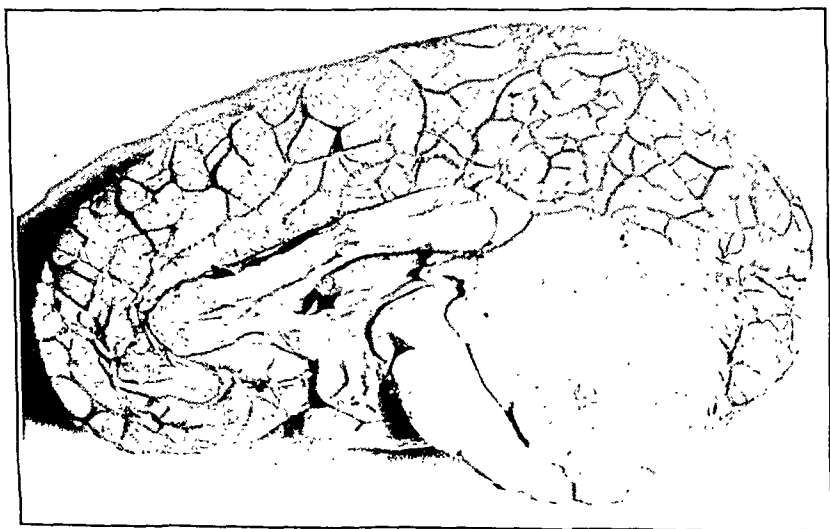


FIG. 2.—Medullablastoma Postmortem Examination. At autopsy, a tumor was found in the vermis of the cerebellum. When the brain was cut into sections after hardening, the tumor was found to measure approximately 5 cm. in diameter; it was of spongy consistency not definitely infiltrating in character and apparently arose from the region of the roof of the fourth ventricle. Examination of the ventricles did not show any enlargement as from an hydrocephalus, and the other tissues of the brain were found to be normal. The meninges were not involved.

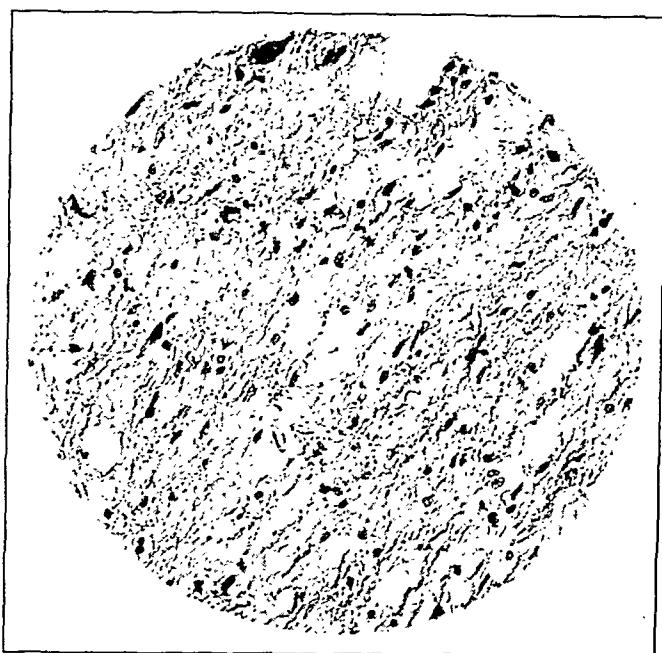


FIG. 3.—Astrocytoma. It will be noted that the tumor is of loose construction and is composed essentially of astrocytes with neuroglia fibrillæ and scattered nuclei and there are areas of cystic degeneration.



FIG. 4.—Astrocytoma. G. W., aged ten years, from the service of the Orthopædic Hospital had a history for over one year of a slowly increasing headache, diplopia, visual defect and epileptiform attacks and with a choked disk of 3 to 6 diopters and retinal hemorrhages. No history of vomiting. At operation a right parieto-occipital subcortical glioma was found which on pathologic examination proved to be a fibrillary astrocytoma.

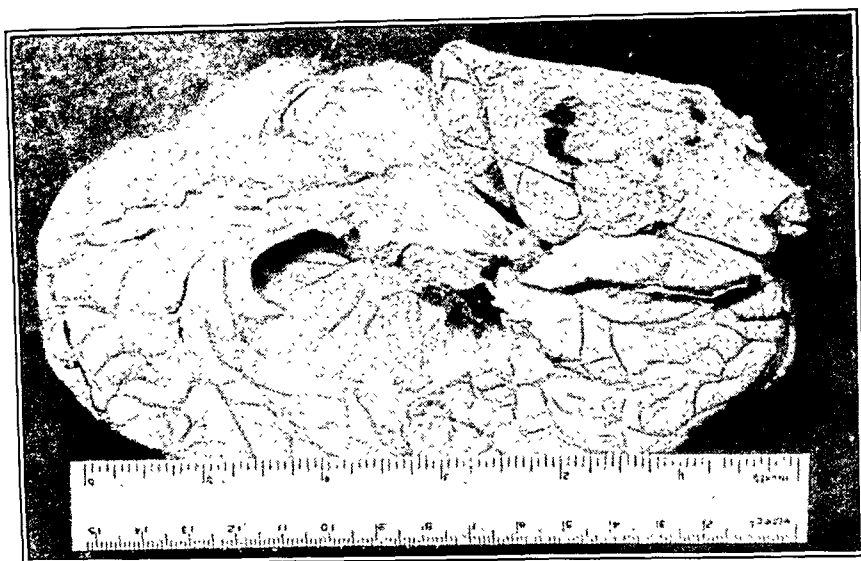


FIG. 5.—Spongioblastoma. This patient was aged two years and from the service of the Children's Hospital. Much antemortem confusion existed concerning her diagnosis. Tuberculous meningitis, tuberculoma, encephalitis, lead poisoning and brain tumor were some of the various diagnoses made prior to autopsy. She showed the usual symptom complex of a midcerebellar glioma lesion heretofore referred to. The internal hydrocephalus resulting from pressure on the iter is clearly shown.

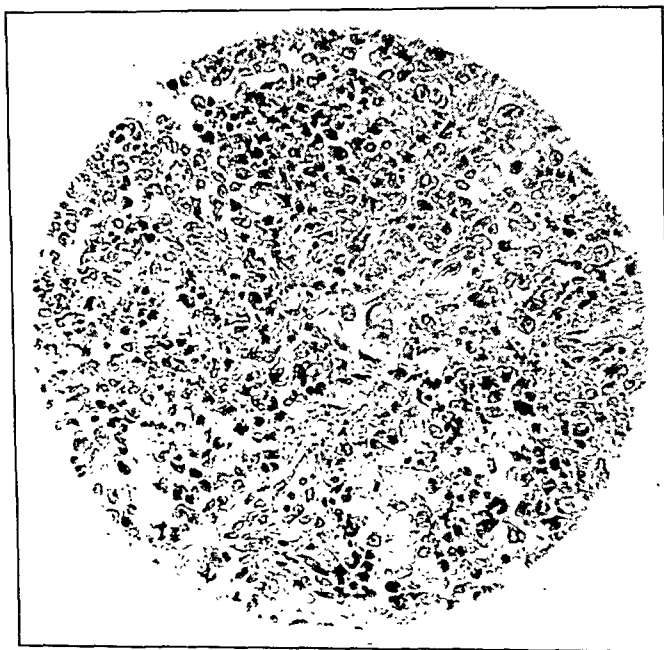
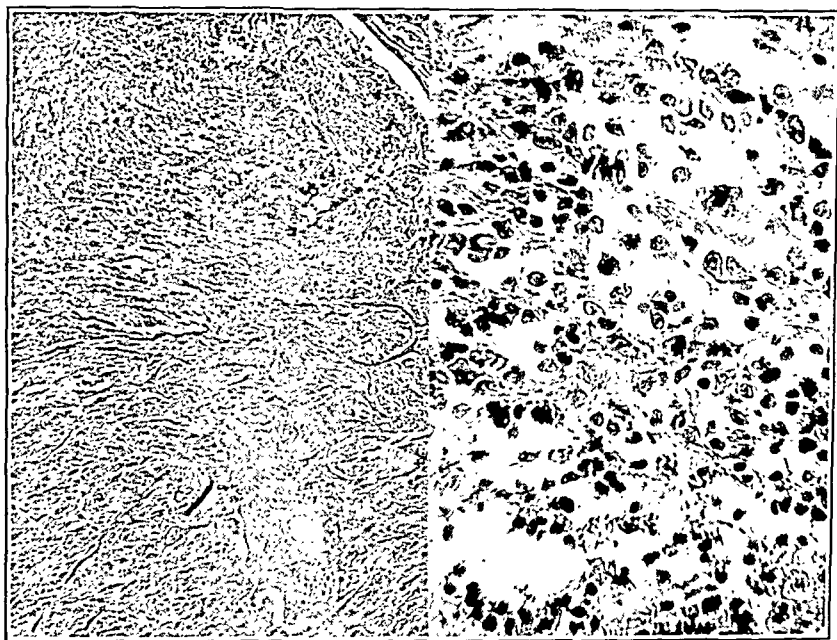


FIG. 6.—Spongioblastoma. The cells are markedly irregular in appearance and their nuclei vary greatly in size and shape and true giant cells are found. Mitotic figures are numerous and round, long, pear-shaped and even star-shaped cells are found. Extensive hemorrhages frequently occur into these lesions due to hyalin degeneration of the walls of the bloodvessels. This tumor is in the midst of cerebellar tissue. It consists of an irregular collection of cells that are of a glial nature. They have irregular oval nuclei, with a tendency to palisade arrangement. The cytoplasm is fairly distinct. No large cells such as giant cells are to be seen. Microscopic diagnosis: Glioma—spongioblastoma.



FIGS. 7 and 8.—Medullablastoma. Report of microscopic observations: "The tumor comes under the general heading of gliomas. The types of cells present vary, but for the most part they fit in with what has been described by Bailey and Cushing as 'medulloblastomas,' but other glial-type cells are present, as is common in this type of tumor. Neuroblasts and spongioblasts are present to a small degree. The connective-tissue stroma, which has a tendency to divide the tumor up into small islets, is a little more abundant than in the usual blastoma."

The astrocytoma contains astrocytes of the protoplasmic or fibrillary types. The protoplasmic type is a soft, quickly degenerating, cystic type of tumor. No fibrillæ can be demonstrated. The fibrillary astrocytomas are a very common tumor composed of fibrillary cells. They show many neurologia fibrillæ and scattered nuclei. Very few blood vessels are seen. They are prone to cystic degeneration, and they are in general of a very loose construction.

*C. Spongioblastomas.* Other histopathologic types of glioma quite common in childhood are the spongioblastomas, multiforme and unipolare. These tumors are prone to undergo degenerative change as well as having no characteristic architecture.

*D. Pseudohydrocephalus.* Numerous cases developing hydrocephalus which have been considered idiopathic in origin, have at necropsy proven to be cases of microscopic gliomas occluding the *iter*. These growths have been sufficient to produce internal hydrocephalus but not large enough to be noted macroscopically. Had the patient been able to survive the hydrocephalus for a sufficiently long time, the microscopic growth would have assumed macroscopic proportions.

**Ventriculography and Encephalography.** Ventriculography and encephalography are substantiating diagnostic procedures that are often of very great value as a localizing method in determining whether a tumor be supratentorial or infratentorial and in such instances either of these two procedures may be of great value, but they are at the same time a matter of considerable danger to the patient. I have seen two patients rapidly succumb following encephalographic technique. This operation should only be performed by those who are skilled in its technique and cognizant of its dangers and it is not to be considered a short cut to determine tumor localization. Its value as a diagnostic measure is not by any means equal to the information that may be given by a thorough neurologic examination.

**The Fetal-rest Theory of the Genesis of Tumors.** Inasmuch as a great proportion of these tumors are formed of primitive embryonal tissue it is of interest to surmise as to their genesis. It is known that the cells forming the cerebellum migrate in an extraordinary way during early embryonic life, and it has been thought that in this situation groups of cells may become isolated and retarded in their development and remain in this location as a "fetal rest." Pfleger<sup>10</sup> found such heterotopic cellular groups in the region of the fourth ventricle in 75 out of 400 supposedly normal cerebellums. If cells of this type should multiply in a neoplastic manner then one of the types of gliomata would be the expected type of growth.

**Case Reports.** In further support of this "fetal-rest" theory I wish to refer to two cases of cerebellar tumors occurring in identical twins at the Children's Hospital in Philadelphia. These cases are of interest because of the occurrence of cerebellar tumors in twins that were apparently of the monozygotic or identical type. The illustrations are those of tissue from



the first twin who died. It was impossible to obtain the consent of the parents for the necropsy on the second. However, there is little doubt that the diagnosis of the lesion in the second was cerebellar tumor. The exact location and histopathologic type of this tumor is, of course, not known.

The first twin died in December, 1924, at the age of six and a half years. The second died in March, 1927, when eight and a half years of age. At the time of the death of the first twin the second had not shown any symptoms of illness and because of this, I was unable to obtain measurements of both twins, particularly the patterns of their palms and soles.

My reason for believing that these children were of the monozygotic type was because of their striking similarity. The boys were born at term without artificial aid; both weighed  $5\frac{1}{4}$  pounds; they were so identical in appearance that it was necessary to tie a ribbon around the wrist of John in order to differentiate him from his brother Jules. The similarity as they grew up through babyhood was striking. Both had dark brown curly hair, dark brown eyes, and dark olive skin, and they were of the same size and stature. The boys began to walk at the age of twelve months and to talk at fourteen months; they showed the same mental, physical and emotional characteristics. Both were fond of the same sort of food, and exhibited an extraordinary eagerness to play with fire. The mother said that they were much more mischievous and prone to get into trouble than any of her other children. When they were two years of age, Jules developed bronchopneumonia and following this his physical growth was retarded and John began to outstrip him in height and weight and to become more robust.

CASE I.—Jules, the smaller of the two, was taken sick in October, 1924, with headache, which gradually increased in severity and frequency; this was soon followed by projectile vomiting and disturbance in walking. In the latter part of November he was taken to the Children's Hospital in Philadelphia, where he had several generalized convulsions and where he died on Christmas Day, 1924. Ophthalmologic examination at the hospital had revealed bilateral choked disk with an elevation of from 3 to 4 diopters above the retinal level. The eyeballs were parallel and there were no apparent extraocular palsies. A lumbar puncture had been performed without untoward results. The routine examination of the spinal fluid did not reveal any abnormalities.

*Microscopic Study.* (Dr. N. W. Winkleman, Philadelphia General Hospital.) "The tumor comes under the general heading of gliomas. The types of cells present vary, but for the most part they fit in with what has been described by Bailey and Cushing as 'medulloblastomas,' but other glial type cells are present as is common in this type of tumor. Neuroblasts and spongioblasts are present to a small degree. The connective-tissue stroma, which has a tendency to divide the tumor up into small islets, is a little more abundant than in the usual blastomas."

CASE II.—John, the more robust of the twins following Jules' attack of pneumonia, became sick in September, 1926, with gradually increasing headache, projectile vomiting and disturbance in walking, exactly the same symptoms that the mother had noted in Jules. The boy would suddenly put both hands to his head and scream with pain. This act would frequently be followed by sudden projectile vomiting without nausea. He soon developed a distinctively cerebellar gait and became constipated. About Christmas Day, 1926, he had a series of generalized convulsions lasting several hours and after these attacks he was unable to walk and was confined to bed. Subsequently, he became totally blind in the right eye and the vision of the left eye was limited to perception of light. He developed a skew deviation of the eyeballs and bilateral deafness. The ophthalmologic report of Dr.

Warren Reese showed 4 diopters of choking in the right disk and 3 diopters in the left disk, with marked blurring of each. The family would not permit the child to be taken to a hospital and he died at home in March, 1927.

A review of the literature to date has failed to reveal any recorded instance of cerebellar tumors occurring in identical twins.

Newman<sup>11</sup> states that if twins are alike structurally, they must be alike functionally. A pair of twins with identical brains should have identical mental development at birth, but further mental development depends on training and environment. There is remarkable unity of thought and action in duplicate twins.

Mitchell<sup>12</sup> reported 24 instances of the occurrence of mongolian idiocy in identical twins. His conclusions are that mongolism is a defect of the germ plasm and is against any theory that factors operative during pregnancy are at fault. Mongolism occurring in one of twins, the result of a single ovum pregnancy, has never been demonstrated.

Abt in an article on "Diseases and Fate of Twins," cites many instances of abnormalities, deformities, diseases and defects in similar and dissimilar twins, but does not make any mention of identical cerebellar tumors.

Murray in his treatise on "Twins in Health and Disease," does not mention this condition.

I believe that the identical occurrence of cerebellar tumors in monozygotic twins may be construed as evidence supporting the constitutional factor in, and especially the "fetal rest" theory of, the development of neoplastic tissue. There can be little doubt that the twins had cerebellar neoplasms in similar situations, and, as it is believed that monozygotic twins develop as a result of the splitting of a single fertilized ovum, I am of the opinion that both of these tumors were due to a "fetal rest" of embryonic tissue remaining there in a quiescent state from the time of the splitting of the original single ovum until some years later when some factor stimulated the neoplastic growth of this group of embryonic cells in each twin.

In further support of the "fetal rest" theory, as noted in the occurrence of similar organic diseases in identical twins, Wolfsohn and Wilson<sup>13</sup> at the 1928 meeting of the American Neurological Association reported four sets of identical twins with identical diseases: (1) Congenital nuclear ophthalmoplegia; (2) Little's disease with similar congenital anomalies; (3) epilepsy and goiter; (4) diabetes mellitus, developing in each twin at fifty-two years of age, and both twins dying at the age of fifty-nine years of an acute apoplexy. These authors emphasize the importance of the conception that identical twins are biologically one individual, physically two individuals.

**Summary.** 1. Brain tumors occur with relative frequency in infancy and childhood.

2. The ratio of juvenile to adult cases in this series is 1 to 14, and their favorite location is in the cerebellum, occurring in this situation in more than 60 per cent of the cases.

3. There is a somewhat general symptomatology: a history of a rather rapid onset in which the child becomes suddenly ill with vomiting and headache, which is soon followed by drowsiness and signs of increasing intracranial pressure as noted by a rapidly developing choked disk with retinal hemorrhages, disturbance of gait, and enlargement of the head and MacEwan's "cracked-pot" sign in infantile cases, plus the localizing symptoms of the growth which may be determined by careful neurologic examination.

4. The usual types of tumors encountered are the tuberculomas, the congenital tumors, and those of the glioma group. Statistics of recent date compared to those of twenty years ago show the lessening frequency of the tuberculous growths. The congenital tumors are generally suprasellar lesions and produce symptoms of dyspituitarism. The glioma group preponderate in childhood both as regards number and malignancy. They are *the* preadolescent tumor and they constitute about 75 per cent of the new growths in preadolescent brains, and 40 per cent of all brain tumors. In childhood they usually occur in the midcerebellar region, arising from the roof of the fourth ventricle and projecting into the vermis. This situation places them in the most critical position to endanger life and to produce an early internal hydrocephalus by pressure on the *iter*.

5. The "fetal-rest" theory of the genesis of neoplastic growths is supported by the identical occurrence of cerebellar tumors in monozygotic twins, as reported in this article.

6. A plea is made for the earlier recognition of cerebral neoplasms in children with obscure head symptoms.

7. Surgical and electrotherapeutic measures are available for the cure and alleviation of distressing symptoms in these patients.

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## THROMBOANGIITIS OBLITERANS:

METHODS OF DIAGNOSIS OF CHRONIC OCCLUSIVE ARTERIAL LESIONS  
DISTAL TO THE WRIST WITH ILLUSTRATIVE CASES.\*

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SEVERAL clinical syndromes of thromboangiitis obliterans have been well described.<sup>1,2,3,4,5,6,7</sup> With the increasing literature on the subject awareness of the disease has been instilled into the consciousness of the physician and it is now more widely recognized. Unfortunately, however, reports of cases diagnosed Raynaud's disease or erythromelalgia, which obviously are cases of thromboangiitis obliterans, are still being issued. The redness of the extremity is attributed to erythromelalgia and the color changes with change in environmental temperature to Raynaud's disease, and yet, color of the extremity and color changes like those of Raynaud's disease are of themselves without value.<sup>2,4,5,6</sup> Reports of the sort mentioned, and others in which inadequate data are given, lend confusion to the literature, and one who reviews it must discard many reports. Such errors are avoidable. There is nothing difficult about the investigation of cases of suspected vascular disease. Accurate diagnosis is not aided by time-consuming mechanical contrivances; they are usually unnecessary. Critical examination by vision and palpation, and simple tests reinforced with an intelligently procured anamnesis, are sufficient.

Thromboangiitis obliterans may be defined as an inflammatory disease of the arteries and veins of the extremities, with resultant occlusion. It is commonly assumed that the palpable arteries are involved (dorsalis pedis, posterior tibial, popliteal, femoral, ulnar, radial, brachial), but this is not necessarily so. These arteries may be normal, but arteries distal to them may be affected. This is logically as well as clinically true, since there is no peculiarity of the disease which indicates that the superficially placed vascular structures must be included in the obliterative process.

Constam has described primary involvement of the upper extremities, with occlusion of the ulnar and radial arteries. Buerger has presented the differentiating points in diagnosis of involvement of the vascular system of the upper extremities. The syndrome of thromboangiitis obliterans, with normal pulsations in the usually palpable arteries, has been described as occurring in the lower extremities.<sup>4</sup> Following, is a presentation of methods of diagnosis of occlusive lesions in arteries distal to the wrist:

\* Work done in the Division of Medicine, The Mayo Clinic. Submitted for publication, February 1, 1929.

**Methods of Diagnosis.** *Involvement of the Ulnar or the Radial Artery.* Occlusion of the ulnar or the radial artery distal to the wrist could not be localized by the usual means, since postural color changes, diminished pulsation of these arteries at the wrist, and lowered cutaneous temperature, might be absent due to the free arterial inflow through the uninvolved vessel. By the following simple test, such a lesion could be accurately diagnosed. The hands of the patient are held in front of him or over his head. The examiner stands at the side of or in front of the patient. If obstruction of the ulnar artery is suspected, the radial arteries are located by their pulsations; the examiner places one thumb lightly over each radial, with the four fingers of each hand behind the patient's wrist,

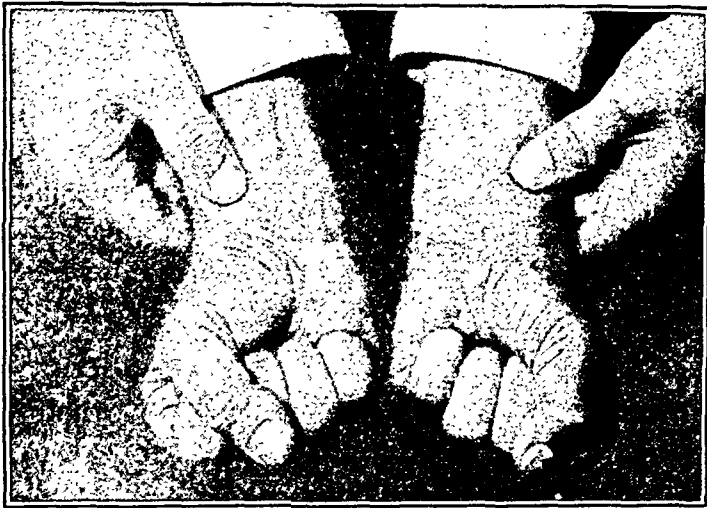


FIG. 1.—First step of the compression test on the radial artery. Blood has been expelled from the hands by clenching them. The fingers of the examiner are about to compress the artery.

thus holding the wrist lightly between the thumb and fingers (Fig. 1). The patient closes his hands as tightly as possible for a period of one minute in order to squeeze the blood out of the hand; the examiner compresses each wrist between his thumb and fingers, thus occluding the radial arteries; the patient quickly extends his fingers partially while compression of the radial arteries is maintained by the examiner. The return of color to the hand and fingers is noted (Fig. 2). In individuals with an intact arterial tree the pallor is quickly replaced by rubor of a higher degree than normal, which gradually fades to the normal color. If the ulnar arteries are occluded, pallor is maintained for a variable period, due to the obstruction to arterial inflow in the two main channels; the radials are obstructed by the examiner's thumbs, the ulnars by the occlusive lesions. Repetition of the test with the examiner's thumbs compressing the ulnar arteries demonstrates the presence or absence of such a lesion in the radial arteries.

The pulsations in the ulnar artery at the wrist are frequently hard to estimate, and this test is of distinct value in suspected occlusion of this artery at or above the wrist. Although usually unnecessary, for pulsations of the radial artery are usually estimated with ease, the test is of value in suspected lesions of the radial artery at the wrist.

*Involvement of the Digital Arteries.* Abnormal postural color changes present in all digits may be due to a lesion more proximal than the digital arteries. Excessive pallor after two minutes of elevation and abnormal rubor after the same period of dependency



FIG. 2.—Second step of the compression test on the radial artery. Arteries have been compressed. Color has returned to the right hand but pallor is prolonged in the left, demonstrating occlusion of the left ulnar artery.

in one or more fingers, to the exclusion of the others, usually means involvement of the arteries of the fingers in which excessive postural color reactions are observed. Irregular distribution of excessive postural color reactions indicates irregular involvement of the digital arteries. Lowered surface temperature of these digits is further confirmation. Other tests of value are the stroke or pressure reaction and determination of the state of pulsations in the digital arteries. The former test is carried out by inducing pallor of the skin of the suspected digit by pressing it for five seconds between the examiner's index finger and thumb or by the examiner stroking the finger heavily, the so-called ironing out of the normal color. In

normal individuals, the induced pallor is replaced by normal or slightly increased rubor as soon as the pressure is removed. In individuals with obstruction of the digital arteries, the pallor is maintained for a prolonged period. The test is best carried out with the hands elevated.

Pulsations of the digital arteries are difficult to palpate. Frequently immersion of the hands in warm water will make pulsations demonstrable. Palpation is best carried out by holding each finger separately, at the base, between the index finger and thumb, in such a manner as to have a palpating finger over the digital artery of each side. Pulsations frequently can be demonstrated subjectively by interlocking the fingers, but localization of an occlusive lesion is difficult. Further aid in the study of lesions of the digital arteries is derived from the use of the sphygmomanometer cuff. A small cuff is wrapped around the base of the finger and inflated well above the systolic blood pressure. Deflation should be slow, and pulsations, if present, are usually felt subjectively as the pressure is lowered below the systolic blood pressure. Oscillations in the needle are, as a rule, not visible. This method does not give sharp results, but is an adjunct to other methods of diagnosis.

**Illustrative Cases.** The first case illustrates occlusion of the left ulnar artery only (Fig. 3a). It is of a right hand and gives the method of demonstration.

**CASE I.**—A Cuban male, a resident of Cuba, was examined at The Mayo Clinic October 10, 1928. He had been an excessive smoker, using about sixty cigarettes and four cigars daily. In October, 1927, there had been gradual onset of moderately severe, aching pain in the fourth and fifth fingers of the left hand. This had been associated with coldness of these fingers and cyanosis under the finger nails on exposure to cold. About the same time, two small, cutaneous nodosities had appeared on the radial side of each of the third, fourth and fifth fingers, one over each phalangeal joint. The condition of the patient had been diagnosed endarteritis obliterans and treatment had been instituted; this had consisted of prohibition of smoking, a milk diet, diathermy, protection from cold, and intravenous medication. In one month all symptoms disappeared, and he returned to The Mayo Clinic only for detailed information regarding his condition. The general physical and complete neurologic examinations, and the usual laboratory tests, including roentgenographic search for cervical ribs, were essentially negative. The hands appeared normal on close inspection, their temperature was normal, and there seemed no change in circulatory efficiency. All arteries of extremities pulsated normally except the left ulnar and right dorsalis pedis arteries, in which pulsations were questionably diminished. The usual methods then failed to demonstrate any definite arterial lesion. The compression test was used on the radial arteries. Appearance of the reddish color was rapid in the right hand, comparing favorably with the normal. In the left hand, a high degree of pallor was present for approximately twenty seconds (Fig. 2), passing then into a light shade of red, gradually deepening, and reaching a color similar to that of the right hand in about one and a half minutes. Repetition of the test with compression of the ulnar arteries instead of the radials disclosed normal return of color in both hands.

**Comment.** The diagnosis of thromboangiitis obliterans was based on the demonstration of a chronic occlusive arterial lesion, apparently of local origin, in an individual who used large amounts of tobacco and who did not have clinically demonstrable arteriosclerosis. All tests for involvement of the digital arteries were negative.

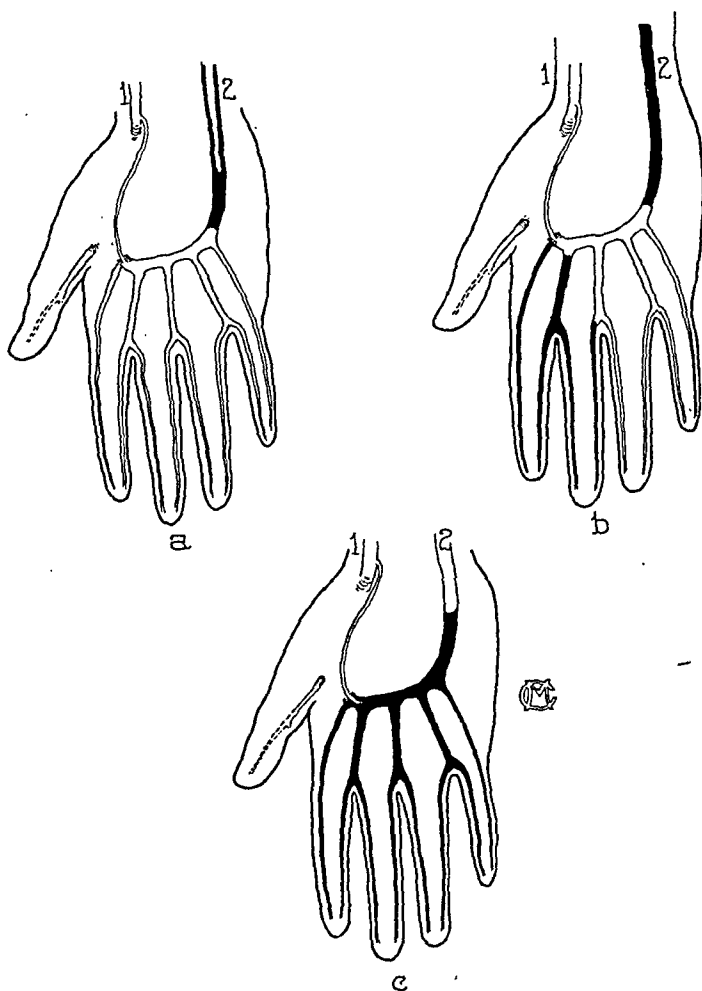


FIG. 3.—The occlusive lesions in the three illustrative cases. Localization is not as accurate as indicated. The radial and ulnar arteries are numbered 1 and 2 respectively.

The second case illustrates occlusion of the left ulnar artery and digital arteries of the right second and third fingers (Fig. 3b).

**CASE II.**—A gentile farmer, aged fifty-seven years, was examined in The Mayo Clinic because of a condition other than vascular disease. For nine years there had been pallor and numbness, on exposure to cold of all distal phalanges, except the thumbs. In a warm atmosphere, normal color quickly returned. The condition had not progressed. General physical and laboratory examinations revealed nothing significant. Pulsations were absent from the left ulnar artery and the compression test on the left radial artery



gave results similar to those described in Case I. . The responses with compression of the left ulnar and right ulnar arteries and of the right radial artery were considered normal. Elevation of the hands for five minutes gave a normal response, except in the second and third fingers of the right hand, where a definite degree of abnormal pallor appeared. These fingers were objectively cold and after pressure had been made on them or the color ironed out, pallor persisted for a prolonged period.

**Comment.** The compression test on the radial arteries localized a lesion in the left ulnar artery. Some evidence of this was given by the absence of pulsations, but recognition of pulsations in ulnar arteries is frequently difficult in individuals with supposedly normal peripheral arterial trees. The compression test is then a valuable adjunct in the recognition of a condition of obstruction in the ulnar artery at the wrist, and in portions of it distal to the wrist. It is of less, but distinct, value in similar involvement of the radial arteries. Abnormal postural color changes, and lowered surface temperature and slow return of color after pressure of the second and third fingers of the right hand indicated occlusion of these digital arteries. The diagnosis lay between arteriosclerotic disease with occlusion and thromboangiitis obliterans. The patient's age is near the upper age limit for thromboangiitis obliterans. His nationality offers no difficulty to such a diagnosis. Although the general impression is that thromboangiitis obliterans is a disease of Hebrews, only about 50 per cent of 300 patients in our series were Hebrews. There was clinical evidence of arteriosclerosis of only a mild degree, and this, coupled with the lack of progression, further favors the diagnosis of thromboangiitis obliterans. Since arteriosclerotic disease is degenerative in nature it is usually progressive; thromboangiitis frequently becomes quiescent.

The third case illustrates occlusion of the distal portion of the right ulnar artery and digital arteries of the second, third, fourth and fifth fingers of the right hand (Fig. 3c), and the pain of finger claudication.

CASE III.—A Scotch-Irish farmer, aged thirty-six years, was examined at The Mayo Clinic December 13, 1928, because of coldness of the fingers of the right hand. He had been a moderate smoker, using a can of tobacco weekly. There was no history of preceding phlebitis, trauma or freezing of the hands. In September, 1928, he had noted that the index finger of his right hand at times became very cold as far proximally as the second phalangeal joint. Shortly after this, the same trouble had appeared in the third, fourth and fifth fingers. Still later he had noted pallor and numbness of these parts after exposure to cold, followed by cyanosis on warming. For a month previous to examination, pain could be induced in the involved fingers by rapid alternate extension and flexion. Ten days before admission he had noted a small, movable mass, about 1 cm. in diameter, in the palm of the right hand. General physical examination and routine laboratory tests revealed nothing that was considered of importance. The pupils reacted slowly to light. Roentgenographic examination of the cervical spine disclosed rudimentary cervical ribs. Neurologic examination revealed dimin-

ished perception to pain, over the palmar surface of the third, fourth and fifth fingers, graded 2, and over the dorsal surface of the right hand, graded 1. This was increased following exposure to cold. The posterior tibial, dorsalis pedis, radial, and ulnar arteries pulsated normally. Tests for vascular insufficiency, such as determination of surface temperature and effects of posture on color, were negative in the feet. When the hands were tightly closed for thirty seconds, then quickly opened, the return of normal color was much delayed in the fingers of the right hand only. When pressure was applied to the ulnar arteries the result was the same. With compression of the radial artery, the entire right hand participated in the delayed response. The second, third, fourth and fifth fingers had a lowered temperature, graded 2 to 3. When elevated for two minutes, pallor graded 1 was present at the distal portion of these digits, but only a minor degree of rubor was evident with prolonged dependency. Further evidence of arterial occlusion was demonstrated by the sphygmomanometer cuff. At no time was there subjective evidence of arterial pulsation of the second, third, fourth and fifth fingers, and the sphygmomanometer needle did not oscillate. The diagnosis was chronic obstructive arterial disease of local origin involving the right ulnar artery and the arteries of the second, third, fourth and fifth fingers of the right hand. The age of the patient makes the diagnosis of thromboangiitis obliterans tenable. The pain in the finger was clearly that of claudication, a rare symptom in this situation.

**Discussion.** The differential diagnosis of diseases affecting the peripheral arteries has been presented elsewhere.<sup>1,2,3,4,5,6</sup> The scope of this paper does not allow presentation of this subject. In brief, the objective evidence of chronic occlusive arterial disease, such as thromboangiitis obliterans and arteriosclerotic disease, rests largely on demonstration of diminution or absence of pulsation in the arteries and on abnormal postural color reactions. Emphasis should be placed on the method of examination. A patient with suspected arterial disease should not be considered completely examined until the patency or occlusion of all arteries possible, the effect of posture on the color, and the skin temperature have been investigated. The condition of patency in arteries is usually determined by palpation of pulsations. This is inadequate alone and handicaps the examiner in cases in which the occlusive lesion is distal to the point of usual palpation. Additional information can be gained from the compression test performed on ulnar or radial arteries, since, by examination of many normal individuals, a fairly constant color reaction has been established. This method is based on the assumption that rapidity of the return of color of the skin after blanching depends on the patency of the deep circulation. Thus, with the radial artery closed by pressure (Fig. 2), the rapidity of the return of color depends on the patency of the ulnar artery. The test is comparable with the circulatory efficiency test, a widely used method. The compression test on the ulnar or radial artery is an additional diagnostic aid and is of distinct value in localizing lesions of the ulnar or radial artery distal to the point of usual palpation at the wrist and in cases in which involvement cannot be definitely demonstrated or excluded by palpation. As such, it is entitled to wider use. The methods

described for demonstrating occlusion of the digital arteries do not always give concise results but are valuable in the examination of suspected cases.

The cases presented demonstrate the patchy nature of the disease: in one instance, there was involvement of the ulnar artery alone; in another, of the left ulnar and the arteries of the right second and third fingers; in still another, the ulnar artery distal to the wrist and the digital arteries of the second, third, fourth and fifth fingers. The cases also illustrate the need for the tests devised since localization could not be accurately made without them.

**Summary.** Methods of diagnosis of chronic obstructive disease of the distal arteries of the upper extremities are presented. Three illustrative cases are presented.

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### THE CAUSE OF ARTERIOSCLEROSIS.\*

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THE study of the etiology of arteriosclerosis has thus far been confined almost entirely to the grosser arteries of the greater circulation. This affords but a limited perspective of the problem; because such a study leaves out of consideration: (1) the incidence and genesis of arteriosclerosis of the pulmonary circulation; (2) observa-

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tions upon capillary sclerosis; (3) sclerosis of the venous system; (4) sclerosis of the valves and the chambers of the heart. An investigation of the lesions in each of these components of the vascular bed throws its own particular light upon the problem of the etiology of arteriosclerosis, so that taken together these evidences bring to my mind fairly convincing proof that intravascular pressure is the main, if not the only cause of arteriosclerosis.

To investigate the etiology of arteriosclerosis by studying the

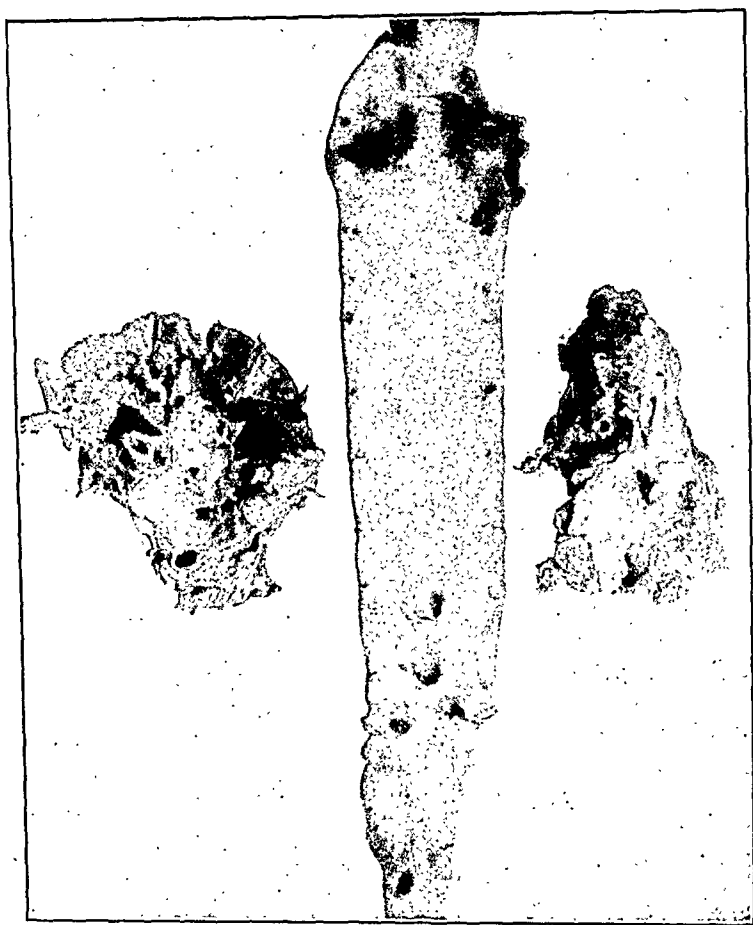


FIG. 1.—Case of hypertension of the lesser circulation (mitral stenosis) in an individual aged twenty-six years, showing normal aorta and intense sclerosis of pulmonary arteries.

arteries of the greater circulation alone, as is the custom, is like trying to understand the architecture of a building by investigating one of the rooms.

**I. Incidence and Genesis of Arteriosclerosis of the Pulmonary Circulation.** The strongest light upon the problem is shed by the observations of arteriosclerosis of the pulmonary circulation. The literature on arteriosclerosis of the lesser circulation is extensive and has been summarized by Ljungdahl,<sup>1</sup> Posselt,<sup>2</sup> Miller<sup>3</sup> and more recently by Schultz.<sup>4</sup> Strangely, the deep significance underlying

the sequence and incidence of pulmonary arteriosclerosis in regard to the broad problem of etiology is not realized, although here and there one finds a stronger or lesser suspicion. The reasons for this failure are: (1) that the study of pulmonary arteriosclerosis has been handled as an isolated problem without relation to the circulation as a whole; (2) because the physiologic conditions underlying the genesis of the arteriosclerosis have not been properly evaluated; (3) because only too frequently the arteriosclerosis has been regarded

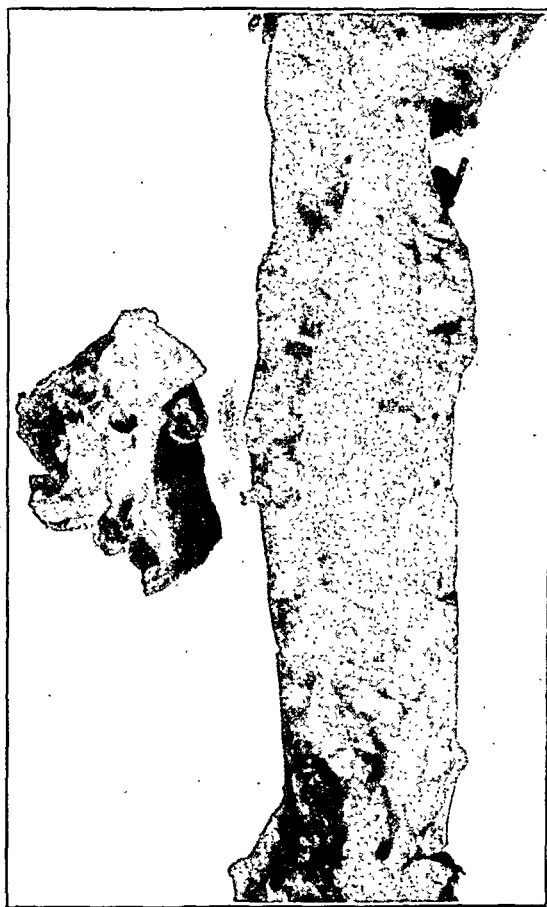


FIG. 2.—Case of hypertension of greater circulation (glomerulonephritis) in an individual, aged forty-two years, showing arteriosclerosis of aorta; pulmonary artery normal.

as a primary phenomenon; (4) because certain supposed causes of arteriosclerosis have not been subjected to sufficient analysis.

Certain facts are sufficiently realized: (1) that arteriosclerosis limited to the general circulation can occur without the slightest evidence of arteriosclerosis in the pulmonary circulation; (2) that arteriosclerosis in the pulmonary circulation can occur without any being present in the greater circulation. These facts must not be regarded as exceptional; they are the usual findings. Examples of each of these instances are shown in Figs. 1 and 2. The conclusion

is inevitable that when such an independence exists, the cause of the arteriosclerosis in one circulation must be absent in the other and *vice versa*; and in the exceptional instance in which it is found in both, the same cause must be operative in both circulations.

In the elucidation of our thesis, it will be best to study the conditions under which arteriosclerosis of the pulmonary circulation occurs. In a previous publication<sup>5</sup> I summarized such conditions. They are, in the order of frequency: mitral disease, long-standing emphysema, cases of marked diminution in lung volume, certain cases of marked scoliosis, pleural adhesions, open ductus Botalli and in communications between the right and left hearts.

The common factor in these conditions is the increase in pulmonary vascular resistance. The mechanisms whereby these lesions produce such an increased resistance are set forth in the earlier publication. The pulmonary circuit is less able to withstand hypertension than the systemic circulation, because the capillaries are more constantly in use, while normally the systemic capillary bed is particularly inactive (Krogh). Furthermore, the collateral circulation between the pulmonary circulation and the aorta is entirely a capillary one between the pulmonary and bronchial arteries (Miller<sup>6</sup>), and offers little outlet for pulmonary pressure.

TABLE I.

Total number of pulmonary arteriosclerosis cases observed during the years 1926 and 1927 equal 50.

During these years there were 770 autopsies which give an incidence of pulmonary arteriosclerosis of 6.5 per cent. Of these 50 cases, 38 (4.9 per cent) showed arteriosclerosis of the greater circulation in addition to arteriosclerosis of the pulmonary circulation.

Twelve (1.5 per cent) showed pulmonary arteriosclerosis alone.

The causes of the pulmonary arteriosclerosis were:

Mitral stenosis (alone)	12 cases
Emphysema (alone)	10 cases
Pleural adhesions (alone)	9 cases
Mitral stenosis and adhesions	3 cases
Mitral stenosis and emphysema	1 case
Emphysema and adhesions	4 cases
Mitral insufficiency	4 cases
Senility	3 cases
Chronic pneumonitis and pleural adhesions	1 case
Mitral stenosis and adhesive pericarditis	1 case
Mitral insufficiency and pleural adhesions	1 case
Pulmonary neoplasm	1 case

In the 12 cases in which arteriosclerosis of the pulmonary circulation alone was found, the causes were:

Mitral stenosis	9 cases
Emphysema	2 cases
Mitral stenosis and adhesions	1 case

All evidence, therefore, seems to show that arteriosclerosis of the pulmonary circulation is practically always secondary to a condition in which increased tension within the lesser circulation can be predicated. Under no other conditions, as far as has been observed, does pulmonary arteriosclerosis occur. The question as to whether pulmonary arteriosclerosis is ever primary will be discussed later.

The clinical features and circulatory dynamics of persistent hypertension of the lesser circulations I have set forth in a previous communication.<sup>5</sup>

**Pathology of Arteriosclerosis of the Pulmonary Artery.** My observations upon 50 cases agree with those of Ljungdahl, Posselt and others that the lesions are identical with those found in arteriosclerosis of the greater circulation. The lesions are diffusely scattered throughout both smaller and larger branches. I cannot subscribe to the observation of Miller,<sup>3</sup> who found in some instances lesions in the smaller radicles with the larger branches practically intact and *vice versa*. As in arteriosclerosis of the greater circulation, the artery is, as a rule, dilated. There is intimal thickening fatty infiltration of the intima, hyperplasia of the elastica, thickening of the media, fatty infiltration in the intima, hyaline change and only rarely calcification.

The infrequency of calcification in arteriosclerosis of the pulmonary vessels is confirmed by many observers, notably Ljungdahl, Fisher<sup>7</sup> and Hornowski.<sup>8</sup> Extensive atheromatous deposits comparable to those seen in advanced arteriosclerosis of the greater circulation are, in my experience, unusual.

In short, the pathology of arteriosclerosis of the gross pulmonary vessels differs from those of the greater circulation only in the mean intensity of the process. The reasons for the lessened intensity of atheroma and calcification in the pulmonary tree are speculative and beyond the scope of this study.

The lesions of the alveolar capillaries in arteriosclerosis of the pulmonary vessels are of profound significance. Strangely, these lesions have been practically ignored in studies of arteriosclerosis of the pulmonary artery. They are not even mentioned in the extensive monographs of Ljungdahl and of Posselt. These capillary lesions are characteristic and pathognomonic of hypertension of the lesser circulation and its attendant arteriosclerosis.

Normally, the capillaries in the wall of the alveolus of an uninjected lung are barely visible. All one notes is here and there a narrow slit, usually filled with a single red blood cell. The wall of the alveolus is narrow, uniform in thickness, and with the exception of an occasional bulge of an alveolar epithelium seen in cross section, the alveolar lining is quite smooth (Fig. 3).

In arteriosclerosis of the lesser circulation, on the other hand, profound changes are noted. The most notable change is a beaded appearance of the alveolar wall (Figs. 4, 5, 6, 7). The beading is the

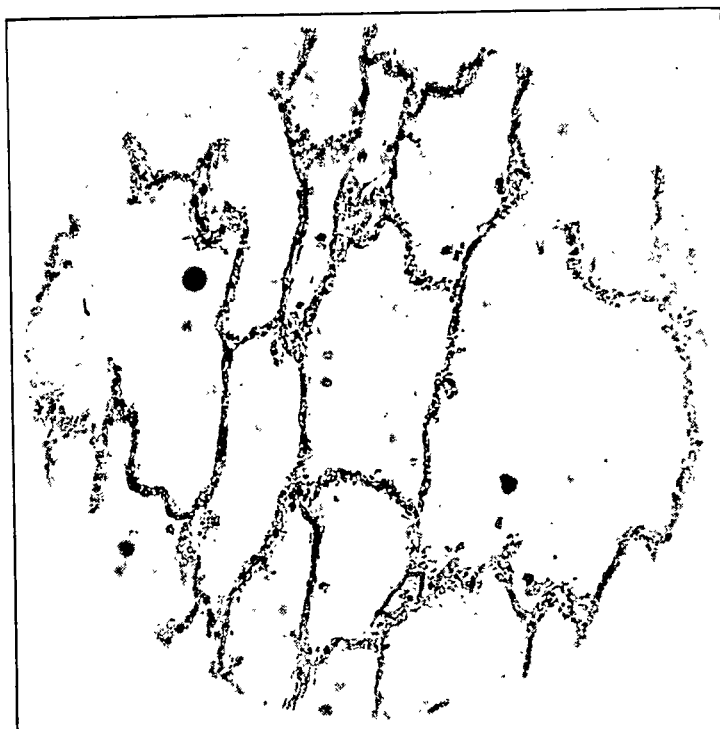


FIG. 3.—Normal lung.

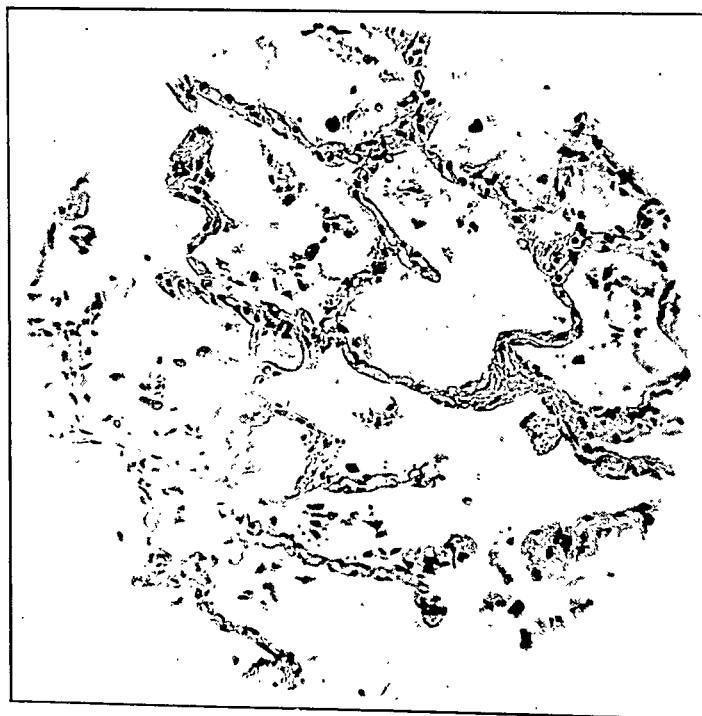


FIG. 4.—Lung in hypertension of the lesser circulation (mitral stenosis) showing beaded appearance of alveolar wall due to dilated and slightly thickened capillaries. Early phase of arteriocapillary fibrosis.



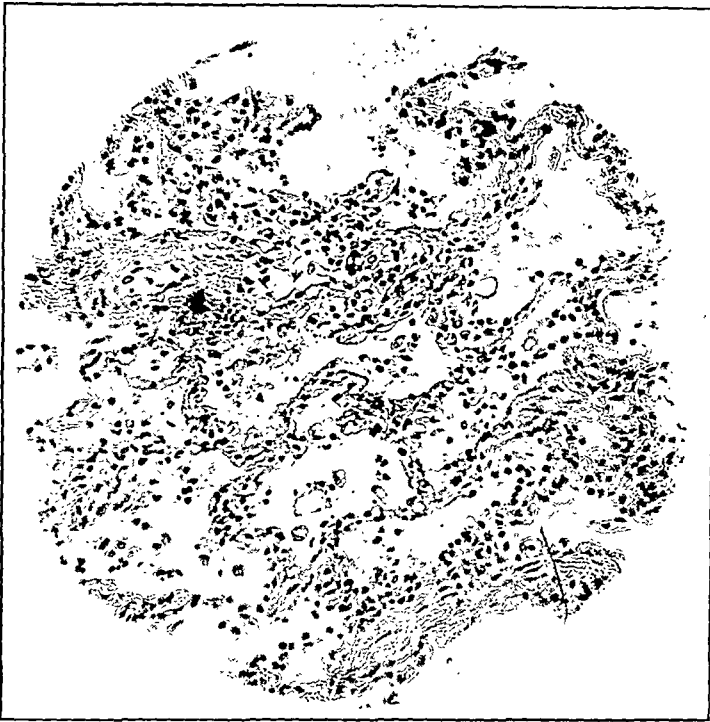


FIG. 5.—Lung in hypertension of lesser circulation (mitral stenosis) showing more advanced stage of arteriopathy, with greater dilatation of capillaries and thickening of the wall. Note bulges of dilated capillaries into the lumen.

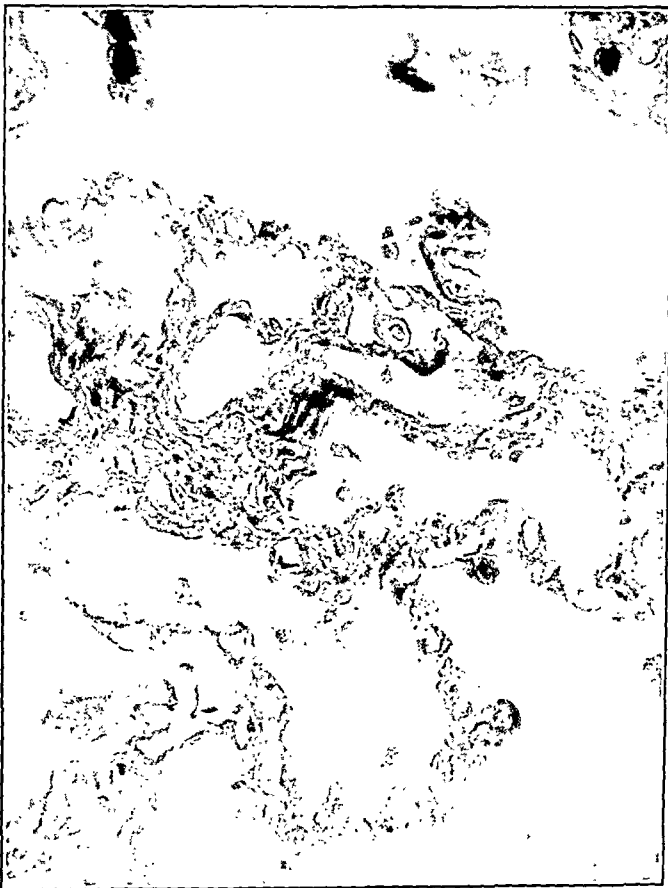


FIG. 6.—High power of arteriopathy of the lung due to hypertension of the lesser circulation (mitral stenosis). Note beaded appearance of the alveolar wall with dilatation and thickening of the capillary wall.



FIG. 7.—High power of arteriocalpillary fibrosis of the lung due to hypertension of the lesser circulation (mitral stenosis) showing more advanced stage. Note marked thickening of capillary walls and bulges into lumen.

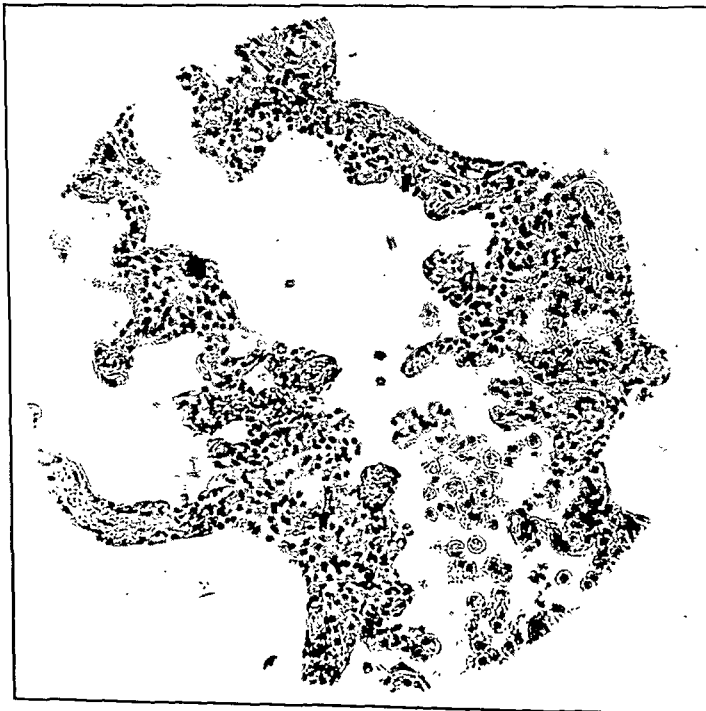


FIG. 8.—Advanced stage of arteriocalpillary fibrosis of the lungs due to hypertension of the lesser circulation (mitral stenosis) showing marked thickening of the alveolar wall, the result of dilatation and marked fibrosis of the capillaries and infiltration with fibroblasts.

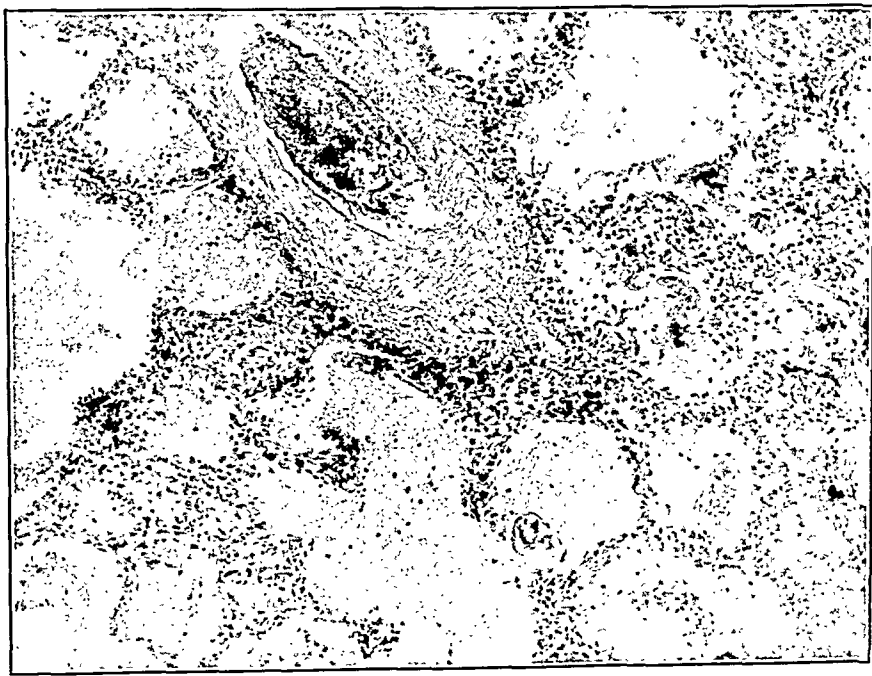


FIG. 9.—Advanced stage of arteriopathy of the lung due to hypertension of the lesser circulation (mitral stenosis) showing marked thickening of alveolar walls due to fibrosis. Note also thickened arterioles.



FIG. 10.—Terminal phase of arteriopathy of the lung due to hypertension of the lesser circulation (mitral stenosis) showing almost complete fibrosis of the lung with transformation into the embryonal type. Note enormous sclerosis of arterioles.



FIG. 11.—Lung from case of uncomplicated aortic insufficiency showing normal histologic structure.



result of enlargement of the capillaries. In advanced cases the enlargement is so great that it forms veritable knobs or peduncles within the lumen of the alveolus (Fig. 8). The enormous extent of the capillary widening can be gauged by noting that many capillaries have room for as many as 6 red blood cells within the lumen. As a consequence of this dilatation there is widening of the alveolar septa with corresponding contraction of the alveolar spaces, which is often extreme in advanced cases. This contraction is undoubtedly one of the reasons for the diminished alveolar capacity observed in most instances of cardiac disease (Peabody<sup>9</sup>). At the same time, the capillary wall is thickened, and in advanced cases, this thickening is considerable. Such thickening must necessarily contribute appreciably to an interference in the exchange of oxygen, and accounts in part for the anoxemia characteristic of hypertension of the pulmonary circuit. In a few cases I have noted distinct hyalinization of the wall of these capillaries, sometimes in considerable stretches of the alveolar walls.

If the disease is of long standing, the increase in pericapillary connective tissue becomes so great that the alveolar wall becomes enormously thickened so that it may give rise to a true interstitial infiltration. This thickening is due not only to the enormous increase in fibrillar connective tissue but also to a cellular infiltration of fibroblasts (Fig. 9).

Finally, in very advanced cases, a true obliteration of alveoli occurs; the newly-formed connective tissue becomes deposited in comparatively enormous masses and the lung morphology reverts to the embryonal type, a change characteristic of all long-standing interstitial changes within the organ from whatever cause, for example, tuberculosis, syphilis, and so forth (Fig. 10). These changes are seen commonly in lungs that have been infarcted, and the transition from the recent infarct to this scar stage can often be traced. Infarction is not the only cause of the great increase of connective tissue. Usually when the latter is present we also find greatly sclerosed arterioles in the neighborhood with marked intimal thickening, so that the lumen is sometimes almost completely obliterated. Unquestionably, therefore, the sclerosis is the result of profound diminution in blood supply.

Summarizing, therefore, the pulmonary lesions of hypertension of the lesser circulation can be described as an arteriocapillary fibrosis, a term first employed by Gull and Sutton.

This is essentially the genesis of the lesions of the so-called "Stauungsinduration" of the lung. Indeed, the resemblance between the lesions of the pulmonary capillaries in hypertension of the lesser circulation and those of the glomerular capillaries in hypertension of the greater circulation (essential hypertension) is striking and in almost every respect they are identical. In the kidney, as in the lung, we find, progressively, thickening of capillary walls, hyaliniza-

tion and eventually connective-tissue transformation, with partial or complete obliteration of the glomerular tuft. In the kidney, also, the interstitium becomes affected with increase in fibrillar connective tissue and round-cell infiltration—the result, as in the lung, of partial or complete closure of the blood supply (MacCallum<sup>10</sup>).

We have every reason for believing, therefore, that the lesions of the kidney associated with essential hypertension resulting in what has been variously called, chronic diffuse nephritis, sclerotic kidney, and so forth, and those of the lung in cases of hypertension of the pulmonary circulation (Stauungsinduration) are identical.

Indeed one can go further and say that in its broader and even finer features the pulmonary lesions here described are the same as the lesions of other viscera commonly noted in patients with hypertension of the greater circulation, notably the changes in the cardiac muscle in coronary sclerosis, in the brain in cerebral arteriosclerosis, and in the pancreas in pancreatic sclerosis (island sclerosis, diabetes).

In other words, arteriosclerosis should be viewed not as a disease of the arteries alone, but as one of the capillaries as well; and its manifestations, clinical and pathologic, are attended by diffuse involvement of most of the parenchymatous organs, especially the kidney, brain and heart, and to a lesser degree, the pancreas. Why the lesion in the greater circulation is clinically greater in one organ than the other is at present unanswerable.

Arterio-capillary fibrosis of the lung, as I have described it, is designated in most treatises as "the lung of heart disease." This is an error, for it is not found in any disorder of the heart that is not attended by an increased pressure in the pulmonary circuit. For instance, it is never found in pure aortic insufficiencies, in which hypertension of the lesser circulation is dynamically impossible. The lung in such instances is normal, as we would expect (Fig. 11). Theoretically, the vital capacity in aortic disease should be greater than in mitral disease. In a recent study, Jones<sup>12</sup> found this to be so.

**Age Incidence of Arteriosclerosis of the Pulmonary Vessels.** The following tables show the incidence in decades:

TABLE II.—ALL CASES OF ARTERIOSCLEROSIS OF THE PULMONARY VESSELS, ASSOCIATED WITH ARTERIOSCLEROSIS OF THE GREATER CIRCULATION.

Decade.	1	2	3	4	5	6	7	8	9	Average age.
My series, 38 cases	..	..	..	3	4	17	8	6	..	57.6
Ljungdahl, 60 cases	1	4	11	8	8	6	8	12	2	49.9

The youngest patient in my series was aged thirty-four years; the oldest eighty-six years.

The youngest patient in Ljungdahl's series was aged twenty-one years; the oldest eighty-six years.

TABLE III.—CASES IN WHICH PULMONARY ARTERIOSCLEROSIS ALONE WAS FOUND.

Decade.	1	2	3	4	5	6	7	8	9	Average age.
My series, 12 cases	..	1	4	3	2	2	..	..	..	36.1
Ljungdahl, 26 cases	1	4	8	9	3	1	..	..	..	29.5
Miller, 18 cases	0	6	2	1	6	3	..	..	..	34.0

The youngest patient in my series was aged sixteen years; the oldest forty-five years.

The youngest patient in Ljungdahl's series was aged nine years; the oldest forty-nine years.

TABLE IV.—CASES OF PULMONARY ARTERIOSCLEROSIS ASSOCIATED WITH MITRAL STENOSIS AND WITHOUT GENERAL ARTERIOSCLEROSIS.

Decade.	1	2	3	4	5	6	7	8	Average age.
My series, 10 cases	..	1	4	2	3	..	..	..	32.7
Ljungdahl, 22 cases	1	4	7	7	3	0	..	..	28.6
Miller, 16 cases	0	6	2	1	4	3	..	..	31.9

The youngest patient in my series was aged sixteen years; the oldest fifty-five years.

The youngest patient in Ljungdahl's series was aged nine years; the oldest forty-nine years.

The youngest patient in Miller's series was aged thirteen years; the oldest fifty-eight years.

TABLE V.—CASES OF ARTERIOSCLEROSIS OF THE GREATER CIRCULATION ALONE.

Decade.	1	2	3	4	5	6	7	8	9	10	Average age.
My series— 195 cases	0	0	2	15	30	67	62	17	1	1	57.3

The youngest patient was aged thirty-one years; the oldest ninety-two years.

These statistics show that the average age incidence of arteriosclerosis of the pulmonary vessels is lower by about twenty years than that of arteriosclerosis of the greater circulation. Furthermore, taking only those cases in which mitral stenosis, the most common cause, is found the age incidence is even a year or two less. In other words, the decades in which arteriosclerosis limited to the pulmonary circulation most commonly occurs, are the third and fourth (in Miller's statistics, the second) while arteriosclerosis of the greater circulation increases as age advances until every one in the fifth and sixth decades reveals such lesions. Obviously the average higher age (49.9) in Ljungdahl's statistics is due to the large number (24) of cases of senile arteriosclerosis of the pulmonary vessels and of cases due to emphysema. In my statistics also the average age is raised by the cases of emphysema.



These statistics lend adequate support for my thesis that it is not age that is the direct cause of arteriosclerosis, but the effects of pressure within the pulmonary artery. If the pressure is raised by an increased peripheral resistance, most commonly a mitral stenosis or an emphysema, arteriosclerosis practically always results no matter what the age may be. In youth, mitral stenosis is the most common cause; in the declining years, emphysema (senile or asthmatic) is the underlying lesion. Furthermore, the small respect that arteriosclerosis has for age is shown by the not uncommon reports of pulmonary arteriosclerosis in infants in whom an increased tension within the pulmonary circulation is produced by a congenital heart lesion, for example, a patent interventricular septum, an open ductus Botalli or a patent foramen ovale. zur Linden<sup>13</sup> reports a case due to patent ductus arteriosus in an infant of eleven months; Wätjen<sup>14</sup> reports one in an infant aged six months due to patent interventricular septum. This case is of especial interest because it proves that a heightened intravascular pressure need last only six months to produce arteriosclerosis. This accords with the observation of Ljungdahl who noted the earliest incidence of pulmonary arteriosclerosis was six to seven months after the cause of the arteriosclerosis appeared.

**Age Incidence of Arteriosclerosis of the Greater Circulation.** Arteriosclerosis, pathologically but not necessarily clinically, is already present at an early age. It is questionable whether the fatty deposits in the intima noted so commonly in infants represents true arteriosclerosis. Most likely they represent lipoid infiltrations due to their high-fat diet (Zinserling,<sup>15</sup> Troitzkaja-Andrewa<sup>16</sup>) and are comparable to similar infiltrations noted in cases of lipemia associated with diabetes (Oppenheimer and Fishberg<sup>17</sup>) in the lipemia of nephritis (Löwenthal<sup>18</sup>), and in experimental "arteriosclerosis" (Anitschkow,<sup>19</sup> Newburgh and Clarkson<sup>20</sup>) produced by a diet rich in cholesterol. Of this, more anon. At all events, the beginnings of true arteriosclerosis in the sense of Jores\* and abundantly confirmed by other observers is noted at an earlier age than we have been accustomed to think. Statistics of autopsies on German recruits in the World War showed that in practically every instance the earlier phases of arteriosclerosis (thickening of the intima, hyperplasia of the elastic fibers, connective-tissue infiltration) are already to be noted in the third decade (Mönckeberg<sup>21</sup>). This I can confirm in my own observations. Furthermore, it is well known

\* "Arteriosclerosis is a complex process in which degenerative and regenerative compensatory hyperplasia of the arterial wall are combined. It leads to widened and tortuous arteries, the walls of which are thickened diffusely and locally, and in which at the same time lipoid, hyaline and lime deposits are found." We might add that the normal change in histological structure of the artery in the young to that found in maturity, consisting in increase in thickness of the intima. The elastica and muscular layer represents a kind of physiological sclerosis to compensate for the progressively increasing intravascular pressure.

that these arterial changes increase both in spread and intensity as the years advance, and in the sixth decade they begin to reveal clinical manifestations (decrement arteriosclerosis of Allbutt).

Now the vast majority of such individuals show no elevation of blood pressure. In advanced years the reading of the sphygmomanometer may show an elevation of 10 to 15 mm. Hg. due to the diminished compressibility of the thickened vessels (Janeway<sup>22</sup>), but it is a common observation that an intravascular pressure when the normal range is entirely compatible with even the most rigid arteriosclerotic vessels. Hypertension is therefore not caused, as had formerly been taught, by arteriosclerosis. Indeed, the relationship is the reverse and all available evidence shows that hypertension in the greater circulation, as in the lesser, is always followed by arteriosclerosis of the vessels no matter how young the patient may be.

Cases of profound arteriosclerosis of the vessels of the greater circulation, due to hypertension associated with glomerulonephritis, are not uncommon in the second and even in the first decades. I have seen a number of such cases. Furthermore, I have reported cases of juvenile and adolescent arteriosclerosis the result of hypertension caused by such peripheral resistances as congenital narrowing of the vessels or congenital stenosis of the isthmus of the aorta. These observations explain why it is that when hypertension exists arteriosclerosis occurs sooner than the normal incidence, and the greater the pressure, the earlier and more intense the lesions are. Such a relation I have noted frequently, and it is conspicuous in all forms of precocious arteriosclerosis, when the inevitable changes of senility can be excluded.

It is not generally appreciated, as it should be, that hypertension is not a new insult that has entered the organism, in the sense, for instance, of an infection, but is a heightened phase of a normal physiologic state, namely, intravascular tension. Such an obvious conception has apparently escaped most observers who have discussed the relation of hypertension and arteriosclerosis. With this premise in mind, we can construct the following syllogism. Hypertension is a heightened phase of normal intravascular tension; there is a definite sequential relation of arteriosclerosis to hypertension in both greater and lesser circulations; such an arteriosclerosis occurs at an early age if hypertension is present and is an inevitable lesion in all individuals past (at least) middle age; therefore normal intravascular pressure may also cause arteriosclerosis provided it acts over a sufficient span of time. The mechanism is analogous to appreciating that a road may be worn down by lighter as well as heavier vehicles; obviously the lighter vehicles will take a longer time. This also explains the reason why decrement arteriosclerosis of the pulmonary artery occurs only at a much more advanced age than decrement arteriosclerosis in the greater circulation. Inas-

much as the normal pulmonary intravascular pressure is only one-sixth that of the aorta, the usual arteriosclerotic changes that occur in the third decade in the arteries of the greater circulation do not arise in the pulmonary vessels until senility. Most of Ljungdahl's cases of senile pulmonary arteriosclerosis were in patients past seventy years (see Table I). There were 3 cases of decrescent arteriosclerosis of the pulmonary artery in my series, the ages of the patient being sixty-seven, seventy-one and seventy-two years. Senescence, therefore, only affects arteriosclerosis insofar as it furnishes a sufficient period to permit the normal pressure changes to take place.

Normal intravascular pressure is the only common factor that explains the universality of arteriosclerosis as a morbid lesion, in all people (including prehistoric), in all climes, in all races, in all ages and in all animals where a heart and vascular system comparable to those of man is present.

*Relation of Arteriosclerosis to Sex.*

TABLE VI.—DISTRIBUTION OF SEX IN ALL CASES OF PULMONARY ARTERIOSCLEROSIS.

	Male.	Female.	Per cent of total autopsies.	
			Male.	Female.
My series . . . . .	23	17	0.72 per cent	0.55 per cent
Ljungdahl's series . . . . .	18	10		
Miller's series . . . . .	22	19		

TABLE VII.—DISTRIBUTION OF SEX IN CASES OF PULMONARY ARTERIO-SCLEROSIS ALONE.

	Male.	Female.
My series . . . . .	5	7
Ljungdahl's series . . . . .	13	14
Miller's series . . . . .	8	9

TABLE VIII.—DISTRIBUTION OF SEX IN ARTERIOSCLEROSIS OF THE GREATER CIRCULATION.

(During the years 1926 and 1927 in Mount Sinai Hospital.)

Total autopsies.		Arteriosclerosis of the greater circulation.			
Male.	Female.	Male.	Female.	Male.	Female.
460	310	154	80	33.5 per cent	25.8 per cent

These statistics fulfill all expectations, according to my thesis. Inasmuch as the normal intravascular tension is greater in males than in females (about 10 to 20 mm. Hg.) we find that the incidence of arteriosclerosis in the greater circulation is greater in males than in females. This is in accord with the findings of all observers. Also, the average age in which arteriosclerosis of the greater circulation is found is higher in females than in males, which is also as we should expect. The average age at death in Mount Sinai Hospital of cases that revealed at autopsy arteriosclerosis of the greater

circulation was 55.3 years in males; 62.3 years in females. Furthermore, the statistics show that the distribution of arteriosclerosis limited to the lesser circulation is divided about equally between the sexes. Inasmuch as pulmonary arteriosclerosis is the result of such diseases as mitral stenosis and of pulmonary lesions that are not more common in one sex than in the other, the almost equal distribution in the sexes also fulfills every expectation. For unknown reasons, there is a slight predominance of mitral stenosis in the female.

The somewhat higher ratio of males as compared with females in all cases of arteriosclerosis, whether in the pulmonary tree alone, or combined with that in the greater circulation, is readily explainable by the higher incidence of arteriosclerosis due to the normal involutinary changes (decreascent arteriosclerosis) within the greater circulation in the male.

We conclude, therefore, that the sex factor, exclusive of the element of intravascular pressure, has nothing whatever to do with the development of arteriosclerosis.

**Additional Evidences of the Relation of Intravascular Pressure to Arteriosclerosis.** 1. Retinal changes associated with hypertension. I have previously shown that the changes known as albuminuric or nephritic retinitis do not occur in any form of renal damage except when hypertension is or has been present. This has also been found by other observers, notably Volhard.<sup>23</sup> Indeed, the best proof that these changes are caused by the hypertension is the observation made by myself and by others (Kollert<sup>24</sup>), in certain cases of healing acute glomerulonephritis. The retinal changes persist during the phase of hypertension; when the latter subsides the retinitis soon disappears. In one instance, followed by me from its inception over a period of four years, I observed the following sequence of events; acute glomerular nephritis, hypertension retinitis; improvement in the patient and disappearance of the hypertension; subsidence of the retinitis; persistence of the albuminuria; in a few months reappearance of the hypertension, which soon reached a high degree; with this a return of the retinitis which persisted until death. So close and consistent is this relation of the retinitis to the hypertension that the term hypertensive retinitis rather than albuminuric or nephritic retinitis is more applicable and has been adapted by many observers accordingly.

Now, it is universally agreed that the lesion of hypertensive retinitis represents an arteriosclerosis of the retinal and choroidal vessels (Collins and Mayou,<sup>25</sup> Cohen,<sup>26</sup> Keith, Wagener and Kernohan.<sup>27</sup> Furthermore, I have noted that a hypertensive retinitis is always coexistent with an arteriosclerosis of all of the vessels of the body. Keith, Wagener and Kernohan in their studies of malignant hypertension (that is, rapidly fatal cases associated with excessive hypertension, normal kidney function and marked retinitis) found

sclerosis of all the vessels of the body including those of the skeletal muscles and gastrointestinal tract. All evidence, therefore, points to the fact that the retinitis is merely the local expression of a diffuse arteriosclerosis and is consequent on the hypertension itself and on no other factor.

We may marshal the following facts in favor of arteriosclerosis being due to circulatory stress:

1. The normal intravascular pressure eventually causes arteriosclerosis of the retinal vessels, while increased tension brings on such lesions earlier and excessive tension (especially diastolic) produces the most profound changes with exudation.

2. Arteriosclerosis is most prominent in those portions of the vascular tree in which stress is greatest, for example, at bifurcations and at points of narrowing, whether normal or abnormal.

3. In cases of congenital stenosis of the aortic isthmus, no matter at what age the patient succumbs, there is always profound sclerosis of the proximal part of the aorta, while the portions beyond show little or no sclerosis.

4. Marchand<sup>28</sup> found no arteriosclerosis in an extremity paralyzed by poliomyelitis, while the healthy limb showed marked changes.

5. The endocardium of such chambers and valves as have been subject to increased or prolonged strain shows changes comparable with those of arteriosclerosis. Those of the right side are involved in hypertension of the lesser circulation, those of the left in hypertension of the greater circulation and in the decrescent or senile periods of life. In mitral stenosis, for instance, it is a common observation that the endocardium of the left auricle is thickened and sclerotic (apart from the thickening due to auricular endocarditis) while the muscle of the auricle is hypertrophied; the left ventricle, on the other hand, shows no change.

6. Arteriosclerosis of the greater circulation is unusual in phthisical subjects in whom the general blood pressure is low. On the other hand, it is exceedingly common in the pulmonary vessels especially when the process is chronic and fibrosing (Ljungdahl,<sup>1</sup> Posselt,<sup>2</sup>) thereby reducing the capillary bed and in turn increasing the pulmonary intravascular pressure.

7. Phlebosclerosis, a lesion histologically identical with arteriosclerosis and absolutely independent of arteriosclerosis (Benda,<sup>29</sup> Simmonds,<sup>30</sup> Schilling<sup>31</sup>), is relatively rare. This is readily understandable when we consider that the pressure in the veins is low or even negative in the greater trunks entering the heart. Even under pathologic conditions intravenous pressures never approach the normal intraarterial pressures; nevertheless, it is a singular fact that whenever phlebosclerosis is found, it has a definite relationship to an increased intravenous pressure.

4. Carrel's<sup>32</sup> demonstration that a sclerosis occurs in a vein sutured between the divided ends of an artery is especially significant because every factor but increased pressure can be excluded.

B. Rokitsansky<sup>33</sup> long ago noted that in chronic congestion of the venous system, when venous pressures are usually elevated, phlebosclerosis is not uncommon. Kaya<sup>34</sup> more recently confirmed this finding.

C. In hypertension of the lesser circulation due to mitral stenosis, I have found that sclerosis of the pulmonary veins is almost as common as the sclerosis of the pulmonary artery. An increased tension in the pulmonary veins can readily be predicated in view of the increased pressure in the left auricle. Ljungdahl<sup>1</sup> and Bruning<sup>35</sup> report similar findings. In emphysema, on the other hand, the pulmonary veins are normal, for the resistance is within the pulmonary capillaries.

D. That phlebosclerosis is exceedingly common in varicosities is universally conceded. In sectioning many varices of the lower extremity, I have found some degree of sclerosis in practically every case. Schilling<sup>31</sup> and Sack<sup>36</sup> found phlebosclerosis three times as frequently in the lower extremity as in the upper. This is accounted for not only by the greater tendency to varicose formation, but by the increased pressure in the lower extremity as compared to the upper.

E. An interesting and suggestive example is that of Cramer<sup>37</sup> who discovered that a patch of sclerosis in the vena cava just above the junction of the iliac veins was not uncommon in elderly individuals, and the older the patient the more common the lesion. Schilling,<sup>31</sup> who made a painstaking study of this lesion, found it in 100 out of 175 autopsies. He describes a circumscribed irregular grayish-yellow area in this region, which occasionally contains lime. In most cases the area is situated on the posterior wall, and the greater the angle between the iliacs the more marked is the lesion. He ascribes the lesion to the impinging of the two currents of blood which occurs exactly at this area; obviously the pressure will be greater, the wider the angle of the iliac junction. He ascribes the predilection of the lesion to the posterior wall to the fact that the vena cava is fixed at this site by inelastic fibrous tissue to the vertebral column. In one case, the lesion was found on the left side of the cava adjacent to an intensely sclerotic patch of aorta to which it was adherent by firm fibrous bands. The question of fixation of the vessel in relation to the genesis of arteriosclerosis will be more fully discussed later. In recent months, I have been able to confirm the frequency of this finding (Fig. 12).

F. One of the most constant associations is that of sclerosis of the portal and mesenteric veins and cirrhosis of the liver (Simmonds,<sup>30</sup> Benda.<sup>29</sup> All observers agree that the sclerosis is due to increased pressure in the portal system the result of the obliteration of the portal radicles within the liver. Mesenteric vein sclerosis has also been reported in the disease described by Baumgarten<sup>38</sup> the result of persistence of the umbilical vein, characterized by a combined splenic and hepatic enlargement, in which the same mechanism of

increased portal pressure enters. Inasmuch as the same lesion, that is, phlebosclerosis of the mesenteric vessels, is common in the so-called Banti's syndrome, one is justified in thinking that hypertension of the portal system may have a part in the causations of the lesions of this disease of mysterious etiology. Indeed, Lossen<sup>39</sup> has suggested this possibility.

G. Intense phlebosclerosis is constantly found in the venous element of an arteriovenous aneurysm (Benda<sup>29</sup>).

8. In the rare cases of congenital communication between the aorta and the pulmonary artery above the cusps, Albrecht<sup>40</sup> found intense sclerosis of the pulmonary artery.



FIG. 12.—Area of phlebosclerosis in the descending vena cava in that position which lies against the aorta and at the junction of the common iliac blood currents.

**“Primary” Arteriosclerosis.** As the word “primary” is usually a cloak for ignorance, it is not surprising that this term is never applied to arteriosclerosis, except in relation to disease of the pulmonary arteries. I have not seen any cases of pulmonary vessel arteriosclerosis which could not be accounted for by one of the lesions causing increased pulmonary artery hypertension set forth above. Ludwig Pick, of Berlin, whose experience is huge, writes me that he also has never seen a case of primary pulmonary arteriosclerosis. Nevertheless, primary arteriosclerosis of the pulmonary vessels (exclusive of syphilis) has been reported, though rarely, and presents the syndrome of hypertension of the lesser circulation. I have subjected most of the reported cases of “primary” arteriosclerosis of the pulmonary artery to critical analysis and conclude that,

if such a lesion exists at all, it is extremely rare (excluding of course the decrescent variety) and can be practically ignored in the study of the subject.

**Experimental Arteriosclerosis.** The subject of experimental arteriosclerosis is so vast that only a résumé of the salient features will be presented. Of all the methods that have been tried there are only two that have stood the test of real consideration: (1) by repeated injections of epinephrin; (2) by feeding with a diet rich in cholesterol.

1. The adrenalin type, first performed by Josué and since repeated by numerous investigators, is now acknowledged to produce only a calcification of the media, identical with that described by Mönckeberg in the extremities of man. The changes in the intima and elastica are slight as compared to those found in conventional arteriosclerosis. The pathogenesis in all likelihood represents a necrosis with secondary calcification. What the relation of the Mönckeberg type of arterial lesion is to true arteriosclerosis is still a debated matter; in any event, the two are certainly different.

2. Cholesterol Arteriosclerosis. In numerous studies Anitschkow<sup>41</sup> and his pupils have described lesions of the vessels which they believed to be true arteriosclerosis in certain animals obtained under a diet rich in cholesterol. These findings have been confirmed by numerous investigators notably by Newburgh and Clarkson.<sup>20</sup> The lesion in the main consists in extensive lipoid deposits in the intima of the size, shape and distribution of true arteriosclerotic patches. That Anitschkow has initiated a real stimulus in pathological physiology cannot be gainsaid, but it is becoming more and more evident that what Anitschkow and his successors have obtained is not true arteriosclerosis but a deposition of lipoid in the intima, similar to that observed in infants who are fed on a diet rich in lipoids (Zinserling,<sup>15</sup> Aschoff<sup>42</sup>) and to that observed by Oppenheimer and Fishberg<sup>17</sup> in diabetic lipemia, and by Löwenthal<sup>18</sup> in the lipemia of "nephrosis."

There are many reasons why the lesions obtained by Anitschkow cannot be accepted as examples of true arteriosclerosis:

1. The lesions have thus far been obtained only in herbivora. Carnivora are not amenable. Anitschkow<sup>43</sup> himself never produced it in dogs, even though a cholesterinemia of considerable degree was induced. Recently Löwenthal<sup>44</sup> claims to have obtained "arteriosclerosis" in omnivora by adding gonadectomy (a procedure which heightens and "fixes" cholesterinemia) to a high cholesterol diet. Shapiro<sup>45</sup> also obtained a hypercholesterinemia and "arteriosclerosis" in rabbits by means of thyroidectomy, splenectomy and gonadectomy, in combination with high cholesterol feeding.

At all events, as Ribbert insists, the conditions under which such an "arteriosclerosis" is produced are so unphysiologic that the normal conditions of the animal's existence does not even approach them.



The cholesterinemia in these experimental animals reaches a far higher degree than that ever obtained under normal conditions.

2. In the arteriosclerosis of man, no such rise in blood cholesterol is ever obtained. In fact, I have never observed any consistent rise in blood cholesterol in arteriosclerosis, and when an increase was present, it could be accounted for by a complication. Indeed, the percentage obtained in animals by a high cholesterol diet is far greater than that obtained in man under practically any conditions, arteriosclerosis or other.

In attempting to reconcile experimental cholesterol "arteriosclerosis" with the mechanical explanation of arteriosclerosis, Schmidtman<sup>46</sup> tried to show that the cholesterinemia caused a hypertension in these animals. Thölldte,<sup>47</sup> employing better controlled methods, could find no such increase. Certainly a high cholesterinemia in other diseases is not associated with a hypertension.

3. I have had the opportunity to study sections of experimental "arteriosclerosis" in rabbits, and in them I have found that the only resemblance to the arteriosclerosis of man is the deposition of lipoid in the intima. There is lacking every evidence of compensatory phenomena seen in human arteriosclerosis; hyperplasia of the elastica, and, in the arteriosclerosis associated with hypertension, hypertrophy of the muscularis. Froboese,<sup>48</sup> Beitzke,<sup>49</sup> and Versé<sup>50</sup> report similar observations.

4. The lipoid depositions are not limited to the arteries of the greater circulation, but are diffusely scattered throughout the tissues of the body, occurring regularly not only in the pulmonary arteries, but throughout the veins and in the reticuloendothelial system. This promiscuity, to my view, is an important argument against the identity between experimental and human arteriosclerosis, for, as I have shown, there is a complete independence in the incidence of true arteriosclerosis, not only between the greater and lesser circulations, but between the arterial and the venous lesions.

5. The lesions of "experimental" arteriosclerosis behave like the lipoid depositions of the arteries and mitral valve observed in infancy (Troitzkaja-Andrewa<sup>16</sup>) in that they disappear (Versé<sup>50</sup>, Beitzke<sup>49</sup>). A disappearance of lipoid infiltration, pathogenetically speaking, we can understand, but the hyperplastic and productive phenomena of arteriosclerosis we cannot conceive as being anything but permanent.

For these reasons, I repeat, an increasing doubt has arisen whether experimental cholesterol "arteriosclerosis" represents human arteriosclerosis. Lubarsch,<sup>51</sup> Ribbert,<sup>52</sup> Beitzke,<sup>49</sup> Froboese<sup>48</sup> and Allbutt<sup>53</sup> deny this identity and this view I also share.

Anitschkow himself apparently is becoming convinced that the cholesterinemia is not the entire story, for in his most recent studies he tries to show that the mechanical factor of pressure is important.

He found, for instance, that only massive doses of cholesterol caused these lesions, while smaller doses produce the same effects only when increased tension is added by injecting epinephrin. Furthermore, by repeating the vital staining experiments of Petroff<sup>54</sup> he found that the lipid material was deposited in the same subintimal areas as were stained by the dye, a circumstance which shows that the imbibition of the substance occurs at points that are under maximal strain. This imbibition also occurs when the vessel is injured from outside. In this connection, Westenhöffer's<sup>55</sup> observations, which I can confirm, are significant. He noted that in the aorta the lipid deposit is earlier and more marked at the site of the prominence of the vertebral bodies where the vessel is in direct contact. These facts are allusive in the interpretation of the pathogenesis of lipid infiltration in arteriosclerosis—a thesis reserved for a later discussion.

Summarizing, experimental arteriosclerosis has thus proven unconvincing and, for reasons submitted, it will surely be unpromising, unless some method is devised whereby a persistent hypertension can be maintained.

**The Relation of Infection to Arteriosclerosis.** The independence in incidence between arteriosclerosis of the greater and of the lesser circulation and the close relation between pressure changes and arteriosclerosis of the pulmonary vessels indicates at once that infection cannot be a factor of much consequence in the production of arteriosclerosis, for the same blood bathes both circulations. It is difficult to conceive that an infection should limit its activities to one circulation to the exclusion of the other and that the adolescent years when infections are more common should be so free from arteriosclerosis. The same argument holds true for toxins, metabolic food products, high-protein diet, etc.

Nevertheless, the infectious origin of arteriosclerosis has always had a wide and serious consideration. One of the fundamental reasons for this is the failure to recognize that every lesion of the vascular system is *not* necessarily arteriosclerosis. Infectious lesions of the arteries are common, but the lesions are those of an arteritis and should not be confused with those of arteriosclerosis, which have all the earmarks of a compensatory reaction.

These remarks require particular emphasis in regard to the relation of syphilis to arteriosclerosis, a relationship that is still regarded as exceedingly close by many clinicians. Turnbull<sup>56</sup> in a recent admirable study summarizes the prevalent current opinion of pathologic anatomists in the statement that syphilis does *not* cause arteriosclerosis, and that the cardiovascular changes of arteriosclerosis are no more common in syphilitics than in nonsyphilitics. This accords with my own observations.

The production of experimental arteriosclerosis by the injection of infectious substances was claimed by Saltykow,<sup>57</sup> but no one, as far as I am aware, has confirmed his findings, namely, that the lesions he obtained are true arteriosclerosis, and not an arteritis.

**Localization and Distribution of Arteriosclerosis.** The apparently unequal and haphazard distribution of the arteriosclerotic lesions in the greater circulation has been advanced as an argument against the thesis that intravascular pressure, which is equally distributed within its own gradient, is the cause. While arteriosclerosis of the greater circulation is always generally distributed, the lesions are more marked in certain regions than in others. The renal, retinal

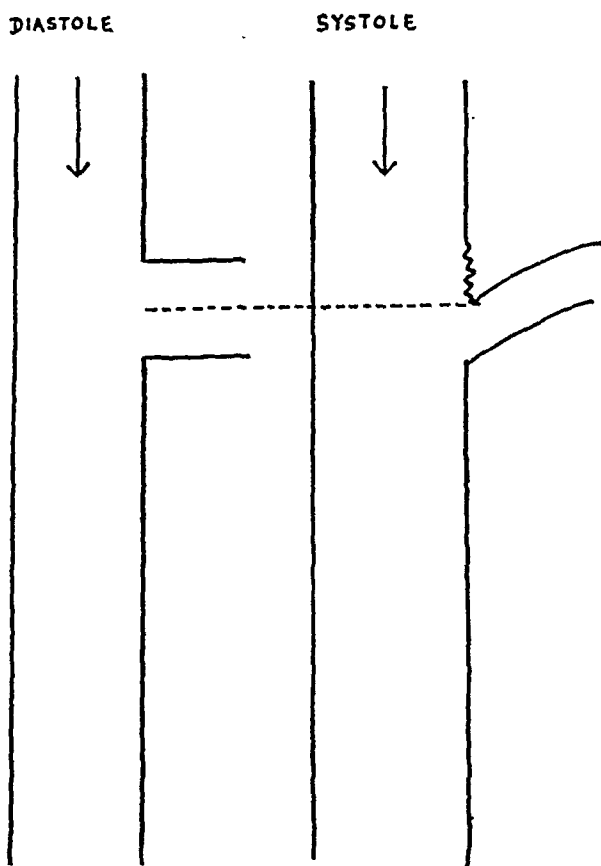


FIG. 13.—Diagrammatic representation showing the effect of fixation of the aorta by the intercostal vessel in the localization of arteriosclerosis.

cerebral, splenic and coronary arteries, beside the aorta, are profoundly affected; the pancreatic and hepatic vessels less so, while the arteries of the skin, the skeletal muscles and the intestines are affected least of all. Furthermore, the patches of arteriosclerosis are not uniformly distributed throughout the vessel and vary widely in intensity in different areas; for instance, they are more prominent on the posterior aspect of the aorta than on the anterior. Apparently, therefore, we must seek other factors for this unequal distribution and localization than that of mere intravascular pressure.

There are a number of observations that indicate that one of the factors is impaired expansile mobility of the vessel, due either to fixation or to external pressure. These observations are the following:

1. The patches of aortic arteriosclerosis occur earliest and are most extreme at or near the origin of the intercostal vessels, which fix the posterior wall of the aorta. Duguied<sup>58</sup> offers a lucid explanation of this predilection. The aorta during systole elongates and stretches away from its cardiac end. At the points of fixation by the intercostal arteries, the stretching of the vessel is hindered. At the proximal side there will be a small area of diminished stretching whereas at the distal side there will be a corresponding area of increased stretching; and it is in the latter areas that the earliest and most extreme arteriosclerosis occurs (Fig. 13).

2. Lauda<sup>59</sup> and Erdheim<sup>60</sup> found in the study of arteriosclerosis of the dural vessels that the patches of sclerosis were most marked, and sometimes even occurred almost exclusively, on the bony aspect of the vessel.

3. Dow<sup>61</sup> in a study of the systemic distribution of arteriosclerosis found that the internal carotid artery in the canal of the temporal bone and in the cavernous sinus presented arteriosclerosis in a very marked degree, and that the vessel wall in this region was usually sacculated. He also found that the radial arteries when affected showed changes just above the wrist, where the vessel lay against the radius, but not higher.

4. The previously mentioned observation of Westenhöffer<sup>55</sup> who showed that the patches of arteriosclerosis in the aorta had a definite relation to the points of fixation of the vessel to the vertebral column, while the hollows between are comparatively unaffected. The patches in a measure give the appearance of a model in relief of the vertebral column.

5. The already cited observation of Cramer<sup>37</sup> and Schilling,<sup>31</sup> who showed that the patch of sclerosis in the lower portion of the vena cava occurred usually at the point of fixation of this vessel.

6. The anterior aspect of the aorta which is free, is much less subject to arteriosclerosis than the posterior, which is more or less fixed by the intercostal vessels and lies, in most of its course, against the rigid vertebral column.

7. The bases of the cusps of the cardiac valves which are firmly fixed are more subject to arteriosclerosis than the free edge. This is an observation emphasized by Libman.

8. When arteriosclerosis of the pulmonary vessels occurs, the earliest and most prominent lesions are in that part of the vessel that lies against the rigid bronchus while that part coursing in the soft pulmonary parenchyma is much less affected and, indeed, is often free from arteriosclerotic changes. This observation is often striking and is important as a confirmation of our thesis (Fig. 14). This observation was discovered by Dr. Martin Schreiber<sup>62</sup> of New York City.

Further investigation is necessary to confirm the factor of fixation and impaired expansile motility in the localization of arteriosclerosis. If this is eventually proven, it will explain why arteriosclerosis is so

comparatively infrequent in the cutaneous and mesenteric vessels, for in these situations the external resistance is comparatively slight.

It must be admitted, however, that neither this factor, nor the more important element of intravascular pressure, accounts for all the vagaries of either the regional or the localized distributions of sclerosis; for they do not explain why there is such a marked difference in its incidence in two parenchymatous organs apparently of

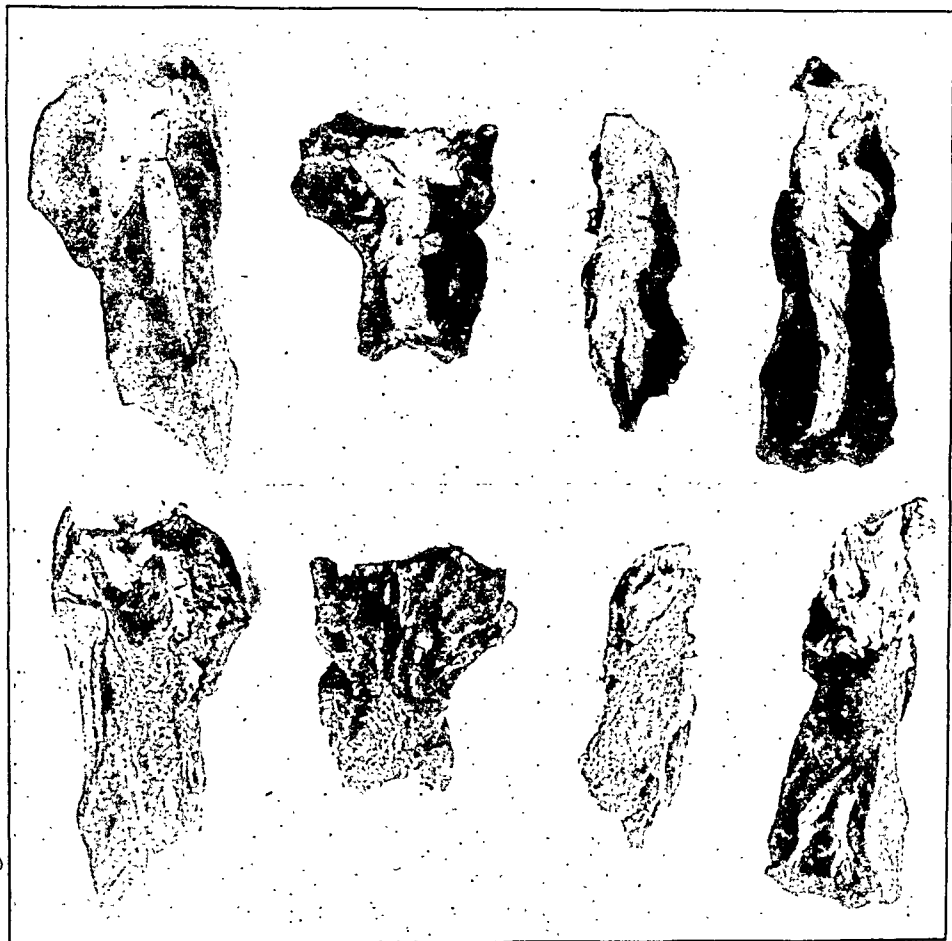


FIG. 14.—Main pulmonary arteries showing localization of arteriosclerosis in that part of the vessel lying against the bronchus.

equal density such as the kidney and the liver. Perhaps it is a question of blood supply, since the kidney has a terminal circulation while the liver has a double supply. This, however, is purely speculative.

**Arteriosclerosis in Animals.** I have had no opportunity to study animal arteriosclerosis, but Krause<sup>63</sup> in an exhaustive monograph, remarks on the gross and histologic identity of arteriosclerosis in the human and in other mammalian animals, on its universality and its increasing prevalence according to age. It is exceedingly

probable, therefore, that the same causes are operative in animals under normal conditions of existence, as obtain in human beings.

**Summary.** 1. The lesions of arteriosclerosis are not limited to the arteries alone, but may affect the veins, the capillaries and the cardiac chambers as well.

2. There is an independence in incidence between arteriosclerosis of the greater and arteriosclerosis of the lesser circulations. As a rule, when arteriosclerosis affects the arteries of one circulation it is absent in the other. It is important, in discussing arteriosclerosis, to know which circulation is affected.

3. Arteriosclerosis of the pulmonary vessels is exceedingly common (6.5 per cent of all autopsies) and occurs practically only when an increased tension within the lesser circulation can be predicated. Practically the only causes are, in the order of their frequency, mitral stenosis, emphysema, pulmonary fibrosis, obliterations of the pleural spaces, kyphoscoliosis, open *ductus Botalli* and communications between the right and left hearts.

4. Inasmuch as hypertension is merely an exaggeration of normal intravascular tension, it is a logical deduction that given a sufficient span of time normal intravascular tension may produce arteriosclerosis. This accounts for the decrescent arteriosclerosis of the greater circulation in man, which begins as early as the third decade, and (because the pressure in the pulmonary artery is one-sixth that in the aorta) of decrescent arteriosclerosis in the lesser circulation in the seventh and eighth decades. Hypertension brings about these changes sooner and more intensively.

5. Age, therefore, affects arteriosclerosis only insofar as it furnishes a sufficient span of time for the normal or the heightened intravascular pressure to act. Inasmuch as the most common cause of increased pressure in the lesser circulation (mitral stenosis) occurs more frequently in the relatively young, arteriosclerosis of the pulmonary circulation occurs at a much lower average age than arteriosclerosis of the greater circulation.

6. Sex has no relation to arteriosclerosis except insofar as it affects pressure relations. Inasmuch as the normal intravascular pressure in the greater circulation is higher in the male than in the female, arteriosclerosis in the greater circulation is more common in men than in women, and the average age in which it is found pathologically and clinically is lower in men than in women. In the lesser circulation, on the other hand, since the causes of the increased intravascular tension are equally common in both sexes, the incidence of arteriosclerosis is equal.

7. In every case of pulmonary arteriosclerosis lesions of the capillaries occur which represent a true capillary fibrosis and these are pathognomonic of hypertension of the lesser circulation. These capillary lesions are identical in genesis and histopathology not only with the sclerosis of the glomerular capillaries that arises in hyper-

tension of the greater circulation, but also with the associated cardiac pancreatic and cerebral hypertensive lesions.

8. This pulmonary capillary sclerosis and its progression represent essentially the lesion of *Stauungsinduration* or pneumonia of heart disease. This lesion is not present in uncomplicated aortic insufficiency, in which an increased pulmonary intravascular pressure is dynamically impossible.

9. The capillary changes, like the lesions of arteriosclerosis in the greater vessels, represent a phenomenon compensatory to the heightened intravascular pressure and the diminution in the capillary reservoir.

10. Other instances of the relation of arteriosclerosis to intravascular tension are cited. These are: *A.* The direct relation of retinitis (arteriosclerosis of the retina) to hypertensive disease. *B.* Arteriosclerosis is most prominent at those sites where the strain is greatest. *C.* Arteriosclerosis occurs most prominently proximal to a congenital or artificial stenosis of a vessel. *D.* The endocardium of such chambers and valves of the heart as have been subjected to prolonged strain show sclerosis. *E.* Arteriosclerosis of the greater circulation is usually less in phthisical patients in whom the blood pressure is notoriously low.

11. Sclerosis of the veins is independent of general arteriosclerosis. It is usually very localized and occurs only when there is a local increase in intravenous pressure of considerable degree. Evidences for this are submitted.

12. "Primary" arteriosclerosis, a term hitherto applied only to that in the lesser circulation, is at best exceedingly rare and has thus far not been proven to exist.

13. Experimental arteriosclerosis as thus far produced is not identical with human arteriosclerosis. The adrenalin type corresponds to the Mönckeberg variety in which the main lesion is a calcification of the media, while the cholesterol type represents merely a generalized imbibition of lipid substance corresponding to the lipid intimal deposits occurring in all forms of hypercholesterinemia. Additional reasons are submitted showing the dissimilarity between cholesterol "arteriosclerosis" and true arteriosclerosis.

14. Infections, including syphilis, are in all probability not the causes of arteriosclerosis, but of an arteritis, different in genesis and histopathology from arteriosclerosis.

15. The independence in incidence between arteriosclerosis of the lesser and of the greater circulations also makes it improbable that toxins, metabolic products, food poisons, and so forth, can cause arteriosclerosis, because the same blood bathes both circulations.

16. Points of fixation and diminished expansile motility of vascular trunks play a rôle in the localization of arteriosclerotic patches.

NOTE.—I thank Dr. Harry Weinstock and Mrs. Mata Roudin for their able help in the preparation of this paper.

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## REVIEWS.

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ARTHRITIS AND RHEUMATOID CONDITIONS. THEIR NATURE AND TREATMENT. By RALPH PEMBERTON, M.S., M.D., Physician to the Presbyterian Hospital, Philadelphia; Associate Professor of Medicine in the Graduate Medical School of the University of Pennsylvania. Pp. 354; 43 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$5.00.

CHRONIC arthritis is the oldest disease of which we have definite records, as Moodie's paleopathologic studies have well demonstrated. The importance of its present-day frequency as a cause of disability would probably be generally admitted, even without the elaborate statistics available to prove this point. The apathy and pessimism toward coping with the condition, that until recently had continued for many years could be only too easily demonstrated during this time by a visit to the chronic ward of any large city hospital. A book, then, that brings together in more detail than is possible in a textbook the existing knowledge on the subject is bound to be welcome, especially when, as is the case with Doctor Pemberton's it is written by one who has contributed perhaps as much as anyone in this country to the recent advances in its study, and when it is so largely successful in substituting for empiricism a rational method of study and treatment which has already produced encouraging results. The medical profession should gladly welcome this first complete presentation of the subject in American literature, with its happy balance between underlying principles and practical applications to treatment. It is obviously far from being offered, however, as the final word on the subject, but rather as a correlation of various factors of suggestive value in the effort more clearly to visualize the subject.

In the discussion of the etiology of chronic arthritis the most important place is properly given to focal infection, though the still existing tendency to carry this influence to extremes is recognized by the author and also does not blind him to the still existing need of searching for the mechanism by which the infection acts (see Section on Dynamic Pathology). The nature of the influence of bacteria is discussed but no conclusions reached; the influence of heredity and constitution is also considered but not finally disposed of.

As regards pathologic anatomy, the simple classification of "atrophic" and "hypertrophic," adopted by the American Committee on Rheumatism, is followed. (These terms correspond to Nichols and Richardson's "proliferative" and "degenerative," or the English "rheumatoid arthritis" and "osteoarthritis" respectively.) Except for terminology, the excellent monographs of Knaggs and Nichols and Richardson are mainly followed.

Under the heading "Dynamic Pathology," in which much of his own work has been done, the author exposes his views of the essential derangements of function in the arthritic syndrome. Basal metabolism, blood nitrogen, uric and lactic acid, the carbon dioxide combining power of the blood, blood calcium, phosphorus, total fat and cholesterol, none show significant changes and thus tend to dispose of such fetiches as the avoidance of red meats, acid foods, and so on. About half of a series of arthritics showed an increase of blood creatin, which sometimes decreased with clinical improvement; more important was the delayed ability in 60 per cent of arthritics to remove sugar in tolerance tests, a disability common to various other disorders, but which here tended to disappear when foci of infection were removed or the arthritis otherwise improved. Diminution of carbohydrate intake therefore seems like a logical step in treatment. Evidence is presented to show that this carbohydrate disability is associated with "denial to the muscular tissues of their usual degree of contact with the circulating blood," a theory that is supported by the improvement that follows physiotherapeutic measures that improve the bloodflow of the affected part.

More than 150 pages are devoted to treatment, doubtless a proper proportion, though with this space available one might properly hope to find room for more definite recommendations, especially in the dietary field. The therapeutic side of the focal infection problem is handled in a progressive yet well-balanced manner. The benefits of the removal of foci are appreciated; and yet, especially in the case of the sinuses, the effect of a serious operation on the general health of the patient coupled with the uncertainty of the effective removal of the focus emphasize the desirability of a conservative attitude. The author considers structural abnormalities of the intestine important and stresses colonic douches with abdominal massage. He finds little or no benefit from acidophilus, nonspecific protein and vaccine therapy, but here statistical support for his views is quite lacking. The section on physiotherapy—treated in considerable sympathetic detail—constitutes one of the best elements in the book.

In the field of dietetics we find: "the use of diet in arthritis consists essentially in a reduction;" but this is offset by emphasizing the need for a proper consideration for the balance of health of the individual. In a given case it is "difficult to determine beforehand what the diet should be." Carbohydrate should be reduced most,

protein next and fat last. Instead of dogmatic directions, a few sample cases are quoted where prompt improvement followed a change of diet as the only treatment instituted.

Having sufficiently expressed his belief in the great value of this work, the Reviewer permits himself a few adverse criticisms that arise on careful reading. Exception may be taken to the rather rambling and jerky method of presentation which at times makes it difficult for the reader to follow the underlying train of thought or acquire definite viewpoints or details of treatment and etiology. One gets the impression that the busy author had not had opportunity to weld together into a united whole the various original reports that have been made by him and his associates over the many years that he has been studying this subject intensively. As a result, one may turn to such a section as treatment, for instance, to find several pages of analyses of symptoms or diagnosis, which might have been at least partly omitted as repetition, or better placed elsewhere. Some sections are advantageously summarized, more are not; the subject matter of the tables—excellent in substance—would often be still more valuable if better arranged and columns more often totaled. Evidence and theories compatible with the author's view sometimes seem (probably due to the author's protracted absorption in the subject) to receive more emphasis than they deserve. Such strictures, however, are slight and unimportant matters that could easily be obviated in another edition. And we hope that such an edition will soon be forthcoming to do its part in bringing up to date the knowledge of the English speaking medical public on a most important subject. E. K.

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FOUR CENTURIES OF MEDICAL HISTORY IN CANADA. By JOHN J. HEAGERTY, M.D., D.PH. Two volumes, totaling pp. 769; 38 illustrations. Toronto: The MacMillan Company of Canada Limited and Chicago: The University of Chicago Press; 1928. Price, \$12.00.

HERE we have a work of double value. Not only is it valuable in the medical history library as an authoritative reference book on such matters as early Canadian epidemics, public health regulations, pioneer physicians, hospital and medical-school foundations; but also it furnishes much delightful medicohistorical reading about that same romantic historical period—perhaps the most romantic on this continent—that Parkman's works have made both familiar and famous. Contemporaries are often allowed to tell their own stories. Thus Cartier's own words tell of the devastating effects of scurvy, while the fate of the settlement at the mouth of the St. Croix is related by Champlain himself. Cochrane's account of the

St. Paul's Bay disease (an extragenitally disseminated syphilis) is given at length and of course the Jesuit Relations play a prominent part. The history of Canadian hospitals offers especially interesting reflections to Americans. For instance, the Hotel Dieu of Quebec was founded in 1639, and seven hospitals in five different cities were in active operation before any were founded in our own country. We congratulate Canada on this addition to her archives and recommend the work most enthusiastically to the historically minded.

E. K.

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THE NEWBORN INFANT: A MANUAL OF OBSTETRIC PEDIATRICS. By EMERSON L. STONE, M.D., Assistant Clinical Professor of Obstetrics and Gynecology, School of Medicine, Yale University, and Attending Obstetrician and Gynecologist to the New Haven Hospital. Pp. 117. Philadelphia: Lea & Febiger, 1929. Price, \$2.00.

THIS is an interesting little book touching upon a topic as often neglected by the larger texts on pediatrics as those upon obstetrics. In it will be found much of value to the obstetrician, his hospital assistants and the general practitioner whose work includes obstetrics. Practically all the injuries, diseases and disorders of the first six weeks of life are gone into in sufficient detail to render recourse to a more encyclopedic treatise unnecessary. The section on feeding, natural and artificial, is well written. A stimulating little monograph on early pathology.

P. W.

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HISTORY OF BLOCKLEY. A history of the Philadelphia General Hospital from its inception, 1731-1928. COMPILED BY JOHN WELCH CROSKEY, M.D. Pp. 765; 15 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$10.00.

THERE have been many historical accounts of this venerable institution which began as the Philadelphia Alms House and Hospital nearly two centuries ago, and moved to its present location in "Blockley Township" in 1833. The hospital became known as "Blockley," a name which is now officially replaced with the more modern designation "The Philadelphia General Hospital." Dr. Croskey has brought together a great deal of widely scattered information, and his "History" is a service to the many students of medicine, physicians, and others who have been connected with old Blockley.

The hospital has just claims of being the oldest on this continent. It has been a teaching hospital for over a century and a half. (It has been estimated that 48,200 medical students have received

instructions in the Philadelphia Hospital between 1772 and 1908). Resident physicians have been in continuous service since 1788. The roll of its attending physicians goes back to 1768; and there are great names indeed on the list of the medical men who have been or are attached to Blockley. The hospital has played an important rôle in the life of Philadelphia since Colonial days. Its history will prove interesting reading not only to physicians and historians, but to many laymen of Philadelphia. The scope of the book may be judged from the table of contents:

Introduction, by John Welch Croskey. The Medical History of the Philadelphia Alms House, by D. Hayes Agnew. The Philadelphia Alms House and the Philadelphia Hospital from 1854 to 1908, by Charles K. Mills. A brief history of the Philadelphia General Hospital from 1908 to 1928, by Joseph Chapman Dqane. The old Blockley Hospital; its characters and characteristics, by J. Chalmers Da Costa. School of Nursing, by S. Lillian Clayton. Biographies of deceased medical men who have been attached to the Philadelphia General Hospital. List of the living medical men who are or have been attached to the Philadelphia General Hospital. George Kierschner—General Hospital mourns its chief. The Philadelphia General Hospital and the War, Charles K. Mills.

Most of the purely historical accounts are reprinted from previous publications; it is gratifying, however, to have them gathered together.

The biographies of the deceased members of the resident and attending staffs have been compiled with care; the source of information of all biographies not compiled by the author has been stated in a footnote. The present Reviewer regrets that Dr. Croskey has merely given a list of the living members of the resident and hospital staff. The information is limited to address, place and date of graduation, and year of residency or of appointment to staff. It would be desirable, though a laborious task, to expand this list into brief biographies after the style used by the publishers of "American Men of Science." This criticism does not detract from the merits of a splendid book.

B. L.

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ORIGIN THROUGH EVOLUTION. By NATHAN FASTEN, PH.D., Professor of Zoölogy in Oregon State Agricultural College. Pp. 456; 75 illustrations. New York: Alfred A. Knopf, 1929.

WITH a belief that the intelligent layman as well as the student should understand the modern conceptions of evolution, the author has presented the scientific evidence and the development of thought concerning this theory in a concise, readable form. Beginning with a statement about the ideas of the origin of matter and the misconceptions propagandists have offered against evolutionary thought,

he outlines the evidence that astronomers, physicists and chemists have obtained about the inorganic development of the earth. Then follows the evidence zoölogy offers from the study of the invertebrates and vertebrates linking the slow development of animal life with the geological and geographical distribution of these forms. The outlined differences illustrate the development of animals phylogenetically. Last, to what one may consider the first part of the book, contribution of comparative anatomy and embryology toward the theory of evolution are mentioned.

The remainder of the book deals with the history of evolutionary thought, the basic and causal factors of evolution as expressed by the agencies of heredity and variation, and the past and future evolution of man. The contribution of Darwin, Weismann, Mendel, De Vries, Galton and others are given adequate consideration. The concluding chapter indicates how the factors of heredity have produced the present stock of human beings, and what eugenics offers for the betterment of the race.

Numerous quotations and references indicate that the author has systematically studied the basis of the theory of evolution, and with scientific accuracy, has developed his arguments logically and in a style that is readily understood. J. B.

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DISEASES OF CHILDREN. First edition edited by SIR ARCHIBALD GARROD, K.C.M.G., D.M., M.A., F.R.C.P., F.R.S., the late FREDERICK E. BATTEN, M.D., M.A., F.R.C.P., and HUGH THURSFIELD, D.M., M.A., F.R.C.P. Second edition edited by HUGH THURSFIELD, D.M., M.A., F.R.C.P., Physician, Hospital for Sick Children, Great Ormond Street, and DONALD PATERSON, M.D., M.R.C.P., Physician to Outpatients, Hospital for Sick Children, Great Ormond Street. Pp. 1106, with two colored plates and 205 illustrations in text. New York: William Wood & Co., 1929. Price, \$13.00.

FIFTEEN years after its original publication, and with a new co-editor, this book appears in its long awaited second edition. The Reviewer is gratified to know that such an important work is to be perpetuated. It is entitled to a high place among the standard one-volume texts of pediatrics.

In the form of a system, the book is a compilation of articles by thirty-seven widely known contributors. While each subject has been brought thoroughly up to date by full consideration of the many recent additions to pediatric knowledge, the retention of much of the matter and actual verbiage of the original work preserves its character.

Because of its conservatism of opinion, its clarity of description and its freshness of style, the Reviewer commends it most highly to the student, the practitioner and the pediatricist. J. S.

PHYSICAL THERAPEUTIC TECHNIC. By FRANK BUTLER GRANGER, A.B., M.D. Pp. 417; 135 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$6.50.

THIS book has not, to quote the author, been written for the specialist in physical therapy. It is rather intended for the physician who has installed a limited equipment.

Beginning with the subjects of electrophysics and physiologic effects produced by electricity the first half of the volume includes chapters on the various electrical modalities, the electromagnetic spectrum, the teaching of physical therapy and a discussion on "a Hospital Department of Physical Therapy." The description of massage and hydrotherapy, limited to only a few pages, is entirely too short to be of any value. The second half deals with the treatment of various pathologic disorders and contains an index of diseases with examples of applications indicated in each particular case.

The text is clear, to the point, authoritative and up to date. The author never indulges in bombast and extravagant claims. Purely theoretical or polemic problems are omitted, the book being essentially of a practical nature. These merits are somewhat offset by the crowding of a wide range of material into a relatively too small space. Numerous excellent illustrations enhance the value of this commendable volume.

J. N.

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TUMORS ARISING FROM THE BLOODVESSELS OF THE BRAIN, ANGIOMATOUS MALFORMATIONS AND HEMANGIOBLASTOMAS. By HARVEY CUSHING, Professor of Surgery, Harvard Medical School and Surgeon-in-Chief, The Peter Bent Brigham Hospital, Boston, and PERCIVAL BAILEY, formerly Associate in Surgery, The Peter Bent Brigham Hospital, and Associate Professor of Surgery, University of Chicago. Pp. 219; 159 illustrations. Charles C. Thomas, Springfield, Illinois, and Baltimore, Maryland, 1929. Price, \$7.50.

THIS monograph is a clinicopathologic study by two investigators who happily are not only surgeons, but pathologists as well. The material upon which this study was based has been in the process of collection for nearly twenty-five years, and the authors are responsible not only for the clinical, but for the pathologic records. It is to be regretted that pathologic anatomy and histology has been neglected by clinicians of the past decade. How fruitful the cultivation of morbid anatomy by the clinician still is amply demonstrated by this splendid monograph. In the introduction is given a list of 1522 histologically verified intracranial tumors; in this large series the hemangiomas of the brain are in proportion to other intra-

cranial tumors as only two to one hundred. The descriptions are excellent and include both the clinical as well as the morphologic aspects of the cases. There are brief but adequate discussions of the various groups. A bibliography of 261 references is given. The monograph may be warmly recommended to neurologists, neurosurgeons, and pathologists. B. L.

THE ORIGIN OF MALIGNANT TUMORS. By THEODOR BOVERI, translated by MARCELLA BOVERI. Pp. 119. Baltimore: The Williams & Wilkins Company, 1929. Price, \$2.50.

THIS little book presents Professor Boveri's earnest endeavor to account for the origin of malignant tumors through perversions of chromosome composition of cells resulting from abnormalities of mitosis. He frankly admits the purely hypothetical aspects of the question and the impossibility with present methods of investigation of reaching a point where we can determine a tumor *in statu nascendi*. But he insists that the cells of a malignant tumor have lost some qualities of normal tissue cells, with resulting capacity for unlimited growth, and that the loss depends upon unequal and abnormal distribution of chromosomes attendant upon tripolar and tetrapolar cell division. The theory is well sustained, but the reader may not experience the same sense of its adequacy that Boveri enjoyed. It lacks something. J. McF.

## BOOKS RECEIVED.

### NEW BOOKS.

- Edema and Its Treatment*.\* By HERMAN ELWYN, M.D. Pp. 82, 3 illustrations. New York: The MacMillan Company, 1929. Price, \$2.50.
- Notes on Chronic Otorrhœa*.\* By A. R. FRIEL, M.A., M.D. (DUB.) Pp. 87; 54 illustrations. New York: Wm. Wood & Co., 1929. Price, \$2.25.
- The Nose, Throat and Ear and Their Diseases*.\* Edited by CHEVALIER JACKSON, M.D. and GEORGE M. COATES, M.D. Pp. 1177; 657 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$13.00.
- The Tonsils and Adenoids and their Diseases*.\* By IRWIN MOORE, M.B., C.M. (EDIN.) Pp. 395; 107 illustrations. St. Louis: C. V. Mosby Company, 1928. Price, \$6.50.
- The Neuroses*.\* By ISRAEL S. WECHSLER, M.D. Pp. 330. Philadelphia: W. B. Saunders Company, 1929. Price, \$4.00.
- \* Reviews of titles followed by an asterisk will appear in a later number.



# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**The Musculature of the Bronchi and Lungs.**—CHARLES CLIFFORD MACKLIN (*Physiological Reviews*, 1929, 9, 1-60). In this review the lung is considered as a muscular organ—a conception which opens up new avenues of approach to clinical problems in this field. Since most of this muscle is related to the bronchial tree and its terminal air chambers, it is spoken of as the bronchial musculature. An accurate visualization of its fundamental architectural plan is necessarily dependent upon a conception of the anatomy of the airway and its terminals, and this is presented, particularly with relation to the “respiratory,” or terminal, part. This has been shown by modern research to be a complicated system of branched tubes whose thin walls are occupied almost completely by rounded apertures leading into other similar branches or into air chambers containing one or more alveoli. The bronchial musculature is a component of the entire airway from the larynx to the alveolar mouths. Incomplete in the trachea, where its thin strands unite the ends of the cartilages, it is, in the main bronchi, a network of transverse and spiral fibers which form a contractile system lying between the cartilages and the mucosa. This formation continues uninterruptedly, becoming progressively finer in build, to the respiratory part of the airway, where the muscle strands form sphincters embracing the aforementioned mural openings, and even edge the partitions of the alveolar sacs. This sponge-work of muscle, because of its peculiar structure and relation to the airway, is in a position, when it contracts, to shorten and narrow the tubes, acting in conjunction with the stretched elastic tissue, and thus assisting in lung deflation. This movement, although it is found throughout the airway, is most marked in the terminal or “respiratory” part, which has an action like that of a bellows, as Keith has pointed out. Relaxation of the muscle, in the inspiratory

phase, allows of dilatation and elongation of the tubes. The bronchial capacity is shown to be variable. It is looked upon as the "dead space." The fundamental lung unit is thus like the lung of lower forms, such as the frog. Innervation, through vagus and sympathetic fibers, coordinates these movements, and it is suggested that there is a reciprocal or "antagonistic" action between the bronchial musculature and that of the chest wall and floor.

A peristaltoid movement of the muscle has been described, which is capable of expelling heavy exudate; indeed it is possible that gentle peristaltic waves are constantly moving toward the larynx.

The very numerous drugs which have been used experimentally upon the bronchial musculature are reviewed, and their actions classified. Adrenalin, which is liberated in increased amounts in asphyxia, has been looked upon as exerting a protective influence by inducing bronchodilatation.

This motor system is discussed with relation to pathologic conditions, as asthma and anaphylaxis. The fine wisps of muscle which occur in the pulmonary interstitium, and which collectively form a tissue of motor significance, are described. In all, 492 separate articles are canvassed.

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**Tabardillo, an American Variety of Typhus.**—MOOSE (*J. Infect. Dis.*, 1929, 44, 186) presents evidence which would make it appear that tabardillo, or Mexican typhus, is a disease between typhus and Rocky Mountain spotted fever, all three of them being closely related but not one and the same. His reason for this belief is based largely upon the result of the injection of material from infected animals into other animals. The animals developed scrotal lesions which the author believes are pathognomonic of tabardillo in guinea pigs. This finding was not observed if the guinea pigs were injected in New York with the blood of patients suffering from mild typhus fever, Brill's disease.

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**The Identity of So-called Agranulocytic Angina. Report of a Case.**—Before presenting their case, ROSE and HOUSER (*Arch. Int. Med.*, 1929, 43, 533) discuss the literature and the cases that have been reported of Schultz's syndrome. They then give in detail the case history, with a full etiologic report. They found that "the lesions common to the various organs were small patches of necrosis without cellular reactions. There was widespread necrosis of the walls and a complete absence of the leukocytes even in the bone marrow. Areas of inflammatory edema were found, especially in the upper respiratory tract and skin." The authors do not believe that agranulocytosis is a specific disease entity because: (1) Marked leukopenia occurs at times in overwhelming infections; (2) the multiplicity and variety of necrotic foci are against the specificity of the angina, while a similar type of necrotic angina occurs in many blood dyscrasias; (3) the disease occurs in both sexes with wide variations in age incidence; (4) a variety of organisms have been recovered from the blood stream and local lesions; (5) nothing has been reported as to the epidemicity of the condition; (6) significant organic lesions have not been found; (7) the disease has not been reproduced experimentally. They suggest the substitution of a more general descriptive term for the present one, giving as examples "sepsis with granulocytopenia" or "agranulocytic infection."

## SURGERY

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UNDER THE CHARGE OF  
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**Embryologic Origin of Club-foot.**—BÖHM (*J. Bone and Joint Surg.*, 1929, 11, 229) state that Bessel-Hagen, the author of the greatest monograph on club-foot advanced the theory that during its embryonic development, the foot passed through no stage of so-called "physiologic club-foot." This belief was endorsed by other investigators and taught authoritatively by Hoffa, but it is untenable. On the contrary, if the deformities of the foot which have been designated collectively as congenital "club-foot" are analyzed into their three chief components, plantar flexion, adduction and supination—one discovers some of these in all of the stages of early embryonic development. All of the clinical manifestations substantiate the conclusion that congenital club-foot is not the result of a mechanical incident, but of a maldevelopment which can be traced back to more deeply lying biologic causes. The author comes therefore to the same conclusion that was reached after the embryologic-anatomic study. The best explanation for the great majority of cases of congenital club-foot is the theory of primary endogenous disturbance of the embryo—an arrest of development.

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**The Remote Results of Gastrectomy.**—GORDON-TAYLOR and DODDS (*Brit. J. Surg.*, 1929, 16, 641) claim that in 52 cases of gastrectomy, no serious alimentary or metabolic upset was found. In 44 per cent of the series a definite anemia was present, but this was discovered through laboratory examinations and was not associated with any symptoms. The anemia does not resemble the pernicious type and no evidence of the occurrence of pernicious anemia can be found in any of the cases. Hydrochloric acid was found in 20 per cent of the series. Fibrin was present in 50 per cent of the feces and there was a general tendency to an increase in the fecal fat. Some increase of the intestinal flora was found, but without increase in any specific type of organism. Cases with a rapid emptying time of the stomach showed a sudden drop in the specific gravity of the urine following the test meal. The importance of the pyloric control of water absorption is hereby demonstrated. An increase in the blood cholesterol and uric acid were the only abnormalities found in the chemical examination of the blood. The bearing of these results on the theoretical considerations of gastrectomy are discussed.

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**The History of the Human Foot and its Bearing on Orthopedic Practice.**—KEITH (*J. Bone and Joint Surg.*, 1929, 11, 10) writes that it is accepted as proved that the human foot has been evolved from one which was prehensile. The condition found in the foot of the

chimpanzee is regarded as the nearest representative of the primitive form from which the feet of man, gorilla and orang have been evolved; that it is function rather than form which has to be studied if we are to trace aright the sequence of changes which has culminated in the human foot; that the arch of the human foot is safeguarded and maintained by the reflex postural action of muscles, ligaments being merely second-line defenses; that flatfoot results from a defect in this defense. The evolution of the various muscles concerned in maintaining the posture of the human foot, the tibialis anticus and tibialis posticus peroneus longus and peroneus brevis and peroneus tertius, is traced from their state in the prehensile foot of apes to their action in the static foot of man. It is shown how the grasping muscles—the flexor longus digitorum, flexor longus hallucis, flexor brevis digitorum—become subservient to the static needs of the human foot. The chief changes that have transformed a prehensile into a plantigrade foot are those of growth—a retrocession of growth affecting the external or plantar limb of the prehensile foot with a progressive growth in its hallucial limb. It is inferred that it was weight of body which compelled man's anthropoid ancestry to assume terrestrial habits of life and that man is the descendant not of a pigmy anthropoid, but one of massive body.

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## THERAPEUTICS

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UNDER THE CHARGE OF

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**On the Vasodilator Action of Small Doses of Iodin and Bromin.**—Clinical experience alone constitutes the basis for the use of iodin in certain forms of arteriosclerosis and on this there is definite divergence of opinion as to its value as a vasodilator. Experimental studies by many investigators have failed to reveal any certain evidence of the supposed dilator action. Now H. GUGGENHEIMER and IRVIN FISHER (*Deutsch. med. Wchnschr.*, 1928, 54, 1959) report briefly the results of their experimental studies employing very weak concentrations of ioidid for perfusion and also for administration to the intact animal as well as their observations with the use of similar minute doses in man. They find in the Langendorff perfused heart that vasodilation first appears with concentration of sodium ioidid of 1 to 100,000 or less. As the concentration is reduced the vasodilator action increases until a dilution of about 1 to 5,000,000 is reached. At the highest dilution the

vasodilator action is optimal. The action even in the perfusion experiments is comparatively slow in development requiring from ten to fifteen minutes before it appears. Cardiac contraction is diminished by iodine and the diminution increases as the concentration of drug rises. Organic preparations of iodine react precisely as do the inorganic salts. Essentially identical results are obtained with perfused vessels. Slow and progressive fall is also produced in nonnarcotized animals by minute doses; thus the blood pressure is significantly reduced in rabbits after the intravenous administration of a dose of 0.2 mg. of sodium iodide, the reduction appearing in about fifteen minutes. Significantly larger doses than this, on the other hand, are without effect upon the blood pressure unless they are large enough to depress the heart. The results from the use of bromine salts are nearly identical with those of iodine, the effective concentrations lying between 1 to 50,000 and 1 to 4,000,000. The exact mechanism responsible for these actions is not known. Applying the results of these experiments to man the authors call attention to the fact that the normal concentrations of iodine in human blood lies between 1 to 8 and 1 to 12 million. This concentration can be raised in man to one effective in producing vasodilation by the administration of a dose of 5 mg. of potassium iodide. Since the increase in blood iodine resulting from this minute dose lasts only a few hours sufficient vasodilation is best maintained by a repetition of the dose three times per day. Although iodine and bromine both act in the same manner, a combination of the two is more effective than is either alone. The authors, therefore, recommend the use of 5 mg. of potassium iodide plus 5 mg. of potassium bromide three times a day in simple aqueous solution. They find this combination particularly effective in cases of mild grades of arteriosclerosis and in patients with hyperpiesia. Small doses of certain hypnotics such as chloral hydrate enhance the vasodilator action of the iodides and the bromides. Hence in more resistant cases they recommend the addition of 0.25 gm. of chloral hydrate to each dose of the foregoing iodide and bromide mixture. They find these combinations are effective in properly chosen cases which comprise chiefly the less advanced stages of arteriosclerosis and of hypertension. In severe cases of arteriosclerosis with cachexia and in well-developed cases of arteriosclerotic contracted kidney the reactivity of the vessels is lost so that no effects can be expected from this form of treatment. Owing to its slight depressant action upon the heart they regard it as contraindicated in cases with evidences of cardiac failure.

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**Spleen Feeding in Joint Tuberculosis.**—On the basis of the accumulated knowledge concerning the biologic effects of the feeding of spleen substance OTTO FLIEGEL (*Deutsche med. Wchnschr.*, 1928, 54, 2053) treated a series of 15 patients with long-standing resistant joint tuberculosis by the administration of small quantities of very lightly cooked calves' spleen. He continued quantities of  $\frac{1}{2}$  to 1 gram of spleen daily for consecutive periods of four weeks, then intermitted for periods of two weeks. These small doses were employed in order to avoid the danger of the production of anemia. Within as short a time as two weeks after the beginning of such treatment he observed reduction in

fever, diminution of secretion from the open lesions and assumption of much more healthy appearance of tuberculous ulcers and the development of fresh, healthy granulation tissue. Local swelling diminished, pain and local tenderness of the joints disappeared and the patients' general condition was improved along with frequent gain in weight. Of 15 patients so treated for periods of time varying from three to five months, 8 showed very marked improvement both in their local lesions and in their general state of health. Five of the 15 patients showed complete local healing. Almost all of these patients had previously undergone all of the usual methods of treatment and were selected for the test because of the proved difficulty in securing favorable response. Fliegel feels that the number of cases is too small to justify conclusions but that the results are sufficiently favorable to warrant an extended investigation of the value of spleen feeding as a supplement to the usual methods of treating joint tuberculosis.

**A New Method of Sterilizing the Bile Passages in Cholangitis and Other Conditions.**—Acting upon the well-known fact that rapid changes in the reaction of the medium are capable of destroying, or of inhibiting the growth of certain bacteria as, for example, in the alkali treatment of pyelitis, K. BECKMANN (*Münchener med. Wchnschr.*, 1928, 75, 2042), applies similar methods in the treatment of cholangitis and in carriers of *bacillus paratyphosus*. Experiments on man and animals carried out by him and others show the possibility of markedly increasing the alkalinity of the bile by the administration through a duodenal tube of 50 cc. of a 5 per cent sodium carbonate solution or of intestinal capsules containing 0.5 gm. of sodium carbonate. Where the capsules are used five are given three times a day, or in the case of the solution 3 doses per day are administered. The treatment in either case is continued for periods of three or four consecutive days. With this treatment two carriers of paratyphoid B were promptly sterilized of their organisms and 1 patient recently recovered from paratyphoid B infection was similarly freed of his bacilli. Two patients with cholangitis and cholecystitis due to the proteus bacillus and one each due to streptococci and *Bacillus coli* were freed of their bacteria as well as promptly relieved of their symptoms. Although the cases so far studied are few in number the author believes the results justify further use of this procedure.

**The Present Status of Lead Therapy in Malignant Disease.**—BELL (*Brit. Med. J.*, 1929, i, 431) advocates that in addition to the beneficial effect of lead when used alone in the treatment of cancer, an aggregate effect is secured when lead and Roentgen rays, and lead and radium are applied within a short time of one another. In selecting patients for treatment with lead, involvement of the liver and kidneys as well as severe myocardial insufficiency, and serious anemia contraindicate the application of lead. As long as the patient is in good condition, with a prospect of about six months of life, other things being equal, treatment may be contemplated. The individual dose should be relatively small with a tendency to increase the quantity of lead to a total amount of 0.5 to 0.8 gm. Suspensions of metallic lead or a colloidal preparation of lead phosphate were used. The material was injected intravenously,

and in a few cases intraärrterially. Intramuscular injections were employed rarely, and ionization with lead of malignant ulcers was also practised. The failure to observe beneficial effects by some investigators is due to the fact that they considered only absolute cures or failures. Moreover, the patients were so ill that treatment could not be completed, or the treatment was so conducted that the patient died as a result of it. Bell emphasizes that "arrest and alleviation of the disease must equally be taken into account." He claims "65 successes out of 303 cases treated—that is 21.5 per cent of successful results." The author also believes that if the cases are carefully selected and the treatment well carried out the method tested has vast possibilities.

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**Tonsillectomy with Diathermy.**—ARON (*Klin. Wchnschr.*, 1929, 8, 167) calls attention to the dangers of hemorrhage following tonsillectomy as well as to the difficulties introduced into the operation by fairly free bleeding and recommends the use of the cold cautery in order to obviate these difficulties. He says that no other method gives such ideal control of bleeding during and following operation. The tonsil is dissected out of its fossa in the usual manner but instead of employing scissors, a knife or a sharp elevator, the flat tip of the cold cautery is used. The only disadvantage of this method seems to lie in the relatively trivial fact that after operation the local reaction in the wound is somewhat greater than that following the ordinary method of dissection.

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## PEDIATRICS

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UNDER THE CHARGE OF

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**The Prognosis of Tuberculosis in Infants.**—GASUL (*Am. J. Dis. Child.*, 1929, 37, 909) studied 404 tuberculous infants, varying in age from four months to two and a half years. These were followed for a period of from one to eight years. When first examined 221 of the 404 showed only a positive tuberculin reaction, 121 showed hilum tuberculosis, 15 showed scrofuloderma, 5 showed papulonecrotic tuberculids, 11 showed a spina ventosa, 6 showed a tuberculous pleuritis, 8 showed an epituberculosis and 2 showed an erythema nodosum. There were fifteen deaths in 404 cases or a mortality rate of 3.71 per cent. Twenty-nine of the 404 infants were infected during the first six months of life. There were five deaths in the 29 cases, or a mortality rate of 17.2 per cent. Seventy-three of the 404 infants became infected with tuberculosis during the second half of the first year of life. There were five deaths or a mortality rate of 6.84 per cent. Seventy-seven of the 404 infants became infected during the first half of the second year. There were five deaths or a mortality rate of 6.49 per cent. None of the infants who had been infected after the first half of the second year died. The fluoroscopic and roentgenologic observations showed either a Ghon tubercle or calcified hilum glands in a certain percentage of all

patients who were followed up for a varying period of years: from seven to eight years, 95.5 per cent; from five to seven years, 90.5 per cent; from five to six years, 66.6 per cent; from four to five years, 71 per cent; from three to four years, 61.8 per cent; from two to three years, 56 per cent; in only 16 per cent of the patients who were followed for one or two years. The location of the Ghon tubercle according to the lobes were as follows: lower lobe of the right lung 33 per cent; lower lobe of the left lung, 20.75 per cent; upper lobe of the right lung, 19.85 per cent; upper lobe of the left lung, 14.15 per cent, and middle lobe of the right lung, 12.26 per cent. The resistance of the infant to a tuberculous infection, even during the first six months of life, is high. An infant with a positive tuberculin reaction or even with definitely recognizable lesion, with the exception of tuberculous meningitis, miliary tuberculosis and ulcerative caseous pulmonary tuberculosis, should not be given a poor prognosis.

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**The Importance of Indicanuria, Fat and Schmidt Fermentation Test in the Practice of Pediatrics.**—FREEMAN, MILLER and FREEMAN (*Arch. Ped.*, 1929, 46, 269) found that the Obermayer test for indican, the Freeman and Miller test for fecal fat and the Schmidt fermentation test are sufficiently accurate and simple to be used in office routine. These tests indicate the character of the food that is the source of trouble and also serve as an excellent control of the results of treatment. Normal children show infrequent indicanuria, fecal fat under 6.5 per cent, and fermentation tests producing less than 4 cc. Children with symptoms of abnormal alimentation practically always show either an indicanuria, an excess of stool fat, or fermentation by the Schmidt test, and in some cases all three of these. In office practice 80 per cent of the examinations in children with symptoms showed carbohydrate excess; 60 per cent protein excess; and 33 per cent fat excess. Dietary restrictions of these cases in accordance with the laboratory findings usually resulted in improvement in the condition of the children, and in the reduction of the abnormalities in the feces and urine.

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**Should Whole Wheat Products Displace the Refined Products?**—LEVINE (*Arch. Ped.*, 1929, 46, 281) claims that the nutritional deficiencies of refined wheat can be overcome by the greater use of supplementary foods. The use of supplementary foods is not being put into practice owing to the costliness of the food necessary to make good the deficiencies of refined wheat flour. The lower the family income the greater is the tendency to use in relatively larger proportions the cheaper foods like wheat and other cereals. In families with small incomes, refined wheat constitutes more than 25 per cent of the total caloric intake and more than 38 per cent of the total protein intake. The other foods entering into the diet do not have sufficient supplementary values and are apt to be poor in some of the essential elements of nutrition found in whole wheat. Children in such families naturally suffer from malnutrition. Since those who need supplementation most are least likely to utilize its advantages, it is important that the type of wheat product forming an unusually large part of the diet should carry all of the factors that are required. The preponderance of those who have no knowledge of the deficiencies of refined flour is overwhelming. There are many who are aware of the deficiencies, but do not know how to



overcome these deficiencies. Supplementation is not practiced widely not for economic reasons but for lack of knowledge. The substitution of whole wheat for the refined product would tend to enhance the nutritional quality of our diet by increasing the intake of iron, of undigestible residue and of several vitamins such as the fat-soluble E and the two water-soluble vitamins, the antiberiberi vitamin and the antipellagra vitamin. The distinctive nutritional value of a cereal is its high residue content, its high mineral content, its high iron content, its richness in the antisterility vitamin and in the antiberiberi vitamin and its relatively fair supply of the antipellagra vitamin. Those who recommend a cereal in the diets of their patients should be well aware of the fact that in advising the use of white wheat they are urging the use of a type of food that has none of the distinctive nutritional qualities of the cereal, but which is merely a mixture of starch and inferior protein.

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**Paroxysmal Hemoglobinuria.**—PURIS (*Am. J. Dis. Child.*, 1929, 37, 1027) states that so-called paroxysmal hemoglobinuria, especially the type caused by chilling, is not really paroxysmal in character. The term is a misnomer, as the condition can always be produced under certain well-defined circumstances in patients subject to it. The condition apparently is due to the presence of a definite special hemolysin in the blood serum of the patient which becomes active at low temperatures. The underlying factor responsible for the presence of the special hemolysin is probably syphilis. It does not seem unreasonable, to suppose that toxins arising from other infections may be capable of bringing about this condition. The Wassermann reaction, observed in the great majority of these cases, may not be due to syphilis, but may be due to the changed conditions of the blood serum. Some of the phenomena observed during the attacks of paroxysmal hemoglobinuria have been ascribed to anaphylactic shock. This is not incompatible with the presence of a special hemolysin in the blood serum. This view is not endorsed by the majority of observers. The only treatment that gives any favorable results is antisyphilitic, but this is frequently unsuccessful as in the case incorporated in this report. The laboratory data in a typical case in a child conform very nearly to the described type.

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**The Incubation Period of Poliomyelitis.**—AYCOCK and LUTHER (*J. Prevent. Med.*, 1929, 3, 103) collected data bearing on the incubation period of poliomyelitis from various sources such as milk-borne infections; cases following tonsillectomy; isolated groups of cases in the same locality where contact could not be traced; cases in which a single known contact occurred; certain instances of multiple cases in families in which the individuals had separated before onset of the disease; and an analysis of all the cases that occurred in 1928 in Massachusetts, with known contact, in which there was an interval of separation prior to onset. In all cases in which the time of exposure can be set within narrow limits, the apparent incubation period falls within a period of from six to twenty days. In all cases in which the last exposure occurred less than six days previous to the onset of the secondary case, the duration of exposure is such that the incubation period could likewise have fallen within these limits. In none of the observations reported was the

incubation period necessarily shorter than six days. In some of these observations there is evidence that the infectious period of the disease may extend from the fourteenth day preceding the onset of symptoms to at least the fifth day of the disease. The incubation period observed in experimental disease in monkeys following the incubation of fully active virus was most often six or seven days, but varied from four to fourteen days. Longer periods of incubation were observed following inoculations of modified virus.

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**The Basal Metabolism of Children of Abnormal Weight.**—TOPPER and MULIER (*J. Am. Med. Assn.*, 1929, 92, 1903) studied the basal metabolism of 70 overweight but otherwise normal children. They found that the majority of these children showed a normal basal metabolic rate, the general tendency being toward the high normal rate. Twenty-nine per cent showed a basal metabolic rate above +10 per cent. Most of these patients with an abnormally high metabolism were between the ages of twelve and fourteen years, the pubertic period. In these cases of a markedly increased basal metabolic rate, there was a greater proportion of girls than of boys. The boys showed this increase of basal metabolism at a somewhat later age than the girls. A certain percentage of the increased metabolic rate in overweight children may be accounted for in part by overfeeding. During the period of puberty many significant changes take place in the child. There is an increase in growth, an increased activity of the endocrine glands and the beginning of sexual life. All of these influence the basal metabolism of the child. The authors believe that there may be a temporary dysfunction of the thyroid gland at this period, which may be manifested by no other sign than the increased basal metabolic rate. If there is an association between prepuberty and an increased basal metabolic rate, the fact that this period occurs somewhat earlier in girls than in boys might account for the greater proportion of girls in this series than boys, showing a marked increase in basal metabolic rate.

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## DERMATOLOGY AND SYPHILIS

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**The Eczema-Asthma-Prurigo-Complex.**—A review of the complexities and identities of certain allergic conditions is given by Low (*Brit. J. Dermat. and Syph.*, 1928, 50, 389) following a careful definition and distinction between prurigo and eczema. The former term is reserved

for Hebra's prurigo, while for the latter he substitutes asthma-eczema to describe the condition often referred to as Besnier's prurigo or Rost's "spätexudatives eczematoid." The work is concerned mainly with the association of asthma-eczema with asthma and ichthyosis, and recounts the evidence in support of their common etiology, heredity and reactions. The author quotes a number of investigators who consistently found a high rate of association among these allergic conditions. In support of a common etiologic factor, a case is given in which sugar was the cause of both the eczema and asthma. The Storm test (extract of scales from the scalp in cases of seborrhea, tested on skins of patients), gave 100 per cent positive reactions in asthma-eczema as against low results in ordinary eczema and seborrheic dermatitis. The high figure is interpreted as conclusive of an allergic diathesis. Keller and Marchionini found that all cases that gave a positive Storm reaction have in addition a diminished power of fixing salicylic acid in the blood similar to that occurring in asthma. Further evidence of close relationship is the occurrence of an eosinophilia in the blood in eczema, asthma and prurigo in the lungs in asthmatics, and in the skin in eczema and prurigo. The author suggests that the explanation for the occurrence of asthma and eczema in alternation is a temporary desensitization in the lung or skin following a reaction in that organ so that further reaction is inhibited. In view of the evidence in favor of a close relationship, the writer points out the surprising thing is not that eczema and asthma may occur in the same patient but that they are not more often associated.

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**Clinical Aspects of Allergy in Dermatology.**—KLAUDER (*Arch. Derm. and Syph.*, 1929, 19, 198) limits the meaning of allergy to hypersensitiveness which in the words of Zinsser is that state in which an individual reacts specifically to contact with a given substance, developing symptoms which are absent upon similar contact in a normal individual of the same species. Clinical phases of hypersensitiveness may be separated into two groups; a group of specific causative sensitization, and a group in which the sensitizing substances are not the cause of the patient's symptoms. He further postulates a "conclusive" hypersensitivity (bacterial sensitization, and specific sensitization ranging from cutaneous to somatic groups) and an "inconclusive" hypersensitivity (nonspecific positive cutaneous tests in conditions of atopy and the exudative diathesis of Czerny and Besnier). Cutaneous hypersensitiveness is manifested by the occurrence of a dermatitis indistinguishable from eczema or by a pruritus attributed to a minimum of exposure or to a slight degree of hypersensitiveness. The mucous membranes are exempt. It is not believed that cutaneous hypersensitiveness exists at birth. Frequent exposure to the exciting substance may be necessary before a frank idiosyncrasy is developed. Certain patients have cutaneous as well as constitutional reactions. This group includes serum sickness, anaphylactic shock, and skin conditions associated with asthma and hay fever. The causes include animal proteins, foodstuffs, pollens, and drugs. Somatic hypersensitiveness is a phase of allergy in which urticaria or angioneurotic edema develops principally after the ingestion of a food substance. Eczema is an uncommon

manifestation of this type except in infancy. A tabulation of a large series of cases of eczema shows a high percentage of nonspecific cutaneous sensitization reactions which may be interpreted as merely an index of heightened irritability in the eczematous skin. The etiology of urticaria presents an additional obscure problem; and the performance of cutaneous tests gives but little aid. The allergic state is more often indicated by the history and symptoms. Hypersensitiveness has probably been overemphasized as a cause of chronic urticaria. The author believes the psychogenic and reflex nervous causes are of equal importance. The allergic state in general is one in which the patient is always hypersensitive to one and usually to a number of protein and non-protein substances. The mechanism of defense, possessed by normal persons, is absent and its absence leads to the state of sensitivity. The symptomatology, once the state is established, appears independent of the presence or absence of the sensitizing substances. This syndrome has much in common with vagotonia as described by Eppinger and Hess. Certain cases are indistinguishable from a disturbed vagotonic balance and often respond clinically to the same drugs, that is, atropin, epinephrin, and calcium. The author quotes Haxthausen's series of 200 patients with skin diseases in which cutaneous tests were done, and in which deletion of the offending substance yielded no appreciable change. These tests are of most value in cases presenting the features of strict cutaneous hypersensitiveness, that is, dermatitis and pruritus.

**The Rôle of Idiosyncrasy and Allergy in Dermatology.**—In addition to tuberculid and trichophytid, BLOCH (*Arch. Derm. and Syph.*, 1929, 19, 175) applies the word allergic to a separate group of skin diseases, namely eczema, drug eruptions, urticaria, Quincke's edema and to other diseases such as serum sickness, asthma and hay fever. The author states that the essence of allergy consists in the ability of the living cell to react to the stimulus of foreign substances (antigens) with the production of specific cellular antibodies. The contact of the antigen with its specific cellular fixed antibody causes a disturbance of cellular life which usually results in an inflammatory reaction. The type and course of the allergic reaction are independent of the nature of the antigen and vary according to the localization of the antibody, that is, the reacting organ. Bloch believes the more pains one takes in the effort to find the cause in cases of eczema in both the history and the functional tests, the more exogenous factors will be found as the real basis for this disease. In his clinic, routine tests are made on every case of acute or chronic eczema with nonprotein eczema-producing substances including formaldehyde, mercury, turpentine, naphthalin, tincture of arnica, primrose, adhesive plaster, iodoform, and quinin. The test substance is rubbed into the intact skin, the area covered with linen and gutta percha, and the test read in twenty-four to forty-eight hours. A positive reaction is indicated by the appearance not only of redness and swelling but the occurrence of papules and vesicles as in eczema. Idiosyncrasy is a more limited term and applies to that small percentage of individuals who react in a characteristic way to an ordinarily nontoxic substance. Bloch, in his experiment with primrose on himself, was able by repeated applications to produce an acquired

idiosyncrasy or hypersensitiveness, and by a concentration of the antigen a typical idiosyncrasy was converted into an allergy. Further chemical work on the active substance of primrose produced a pure crystalline nonnitrogenous substance which was capable in small amounts of exciting a widespread and violent eczema. The author also cites the work of W. Jadassohn on the experimental employment of the antigen (nonprotein) of *Ascaris* in relation to local idiosyncrasy and the antigen-antibody reaction of the Prausnitz-Küstner type. Jadassohn was able to neutralize the *Ascaris* antigen with serum-containing antibodies in accordance with Ehrlich's early principles laid down regarding toxin-antitoxin reactions. The author points out in conclusion the increasing importance of the exogenous factor in the etiology of eczema. The occurrence of an idiosyncratic disease depends on two factors: exposure to an antigenic substance and the capacity of a given organ to produce specific antibodies.

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**Studies in Asthma, VI. Eczema: Its Relation to Allergy.**—O'KEEFE and RACKEMANN (*J. Am. Med. Assn.*, 1929, 92, 883) in classifying the causes of eczema mention toxic, metabolic, and allergic factors. Their report is concerned only with the allergic type of eczema and its relation to the application of the theory of hypersensitiveness. They studied 239 cases of eczema in children and found that 56 per cent of infantile eczema begins during the first four months of life, and 95 per cent before the end of the second year. Skin tests with food and dust allergens were positive in 52 per cent. The cases which were complicated by asthma showed 88 per cent positive skin tests as well as a tendency toward multiple sensitization. In all the positively-reacting children, egg, wheat and milk formed the chief sensitizing foods. Eliminating these foods in the sensitized patients gave improvement in 83 per cent of the cases. Empirically removing the same foods from the diet of the test-negative patients gave improvement in 38 per cent. Dusts were found to be rare as causative factors among children. The duration of the cases seemed influenced by the age of onset, but the average was twenty-five months in the cured cases. A total of 84 cases of adult eczema was studied. The age of onset varied from infancy to sixty years, and the disease was very much more common in women (69.4 per cent). This group as a whole gave 38 per cent positive skin tests. Other manifestations of allergy occurred in 47 per cent of the cases, and in these cases positive skin tests occurred in 70 per cent. By means of the history and skin tests the cases were termed extrinsic, intrinsic, and unclassified. Extrinsic causes were found in 30 per cent and included foods, dusts, animals, plants, drugs and environment. A separate group of seven young men and women constituted an asthma-eczema-hay fever type of general hypersensitiveness. A small number of cases of intrinsic causation were relieved by nose and throat surgical procedures and correction of existing medical difficulties. Unclassified cases of eczema formed the largest group of adult cases. Eighteen of these 53 patients had positive skin tests, while only one was relieved by treatment. The authors believe these positive tests were associated not so much with eczema as with other allergic manifestations which occurred in 13 of the 18 patients.

## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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**Safety Factor in Salpingography.**—The use of iodized oil has become quite popular in outlining various body cavities and canals. The gynecologists were not slow in formulating a technique for its introduction into the tubes and uterus as a preliminary to making a roentgenogram of these organs. The results of these injections have apparently been quite satisfactory in giving a visual record of the size, shape and variations from the normal and have been of special value in aiding the gynecologist to determine the exact point of obstruction in cases where transuterine tubal insufflation has indicated that the tubes were not patulous. In describing their experiences with this procedure, RUBIN and BENDICK (*Am. J. Roent.*, 1928, 19, 348) suggest a few points in the technique which are worthy of notice, especially from the standpoint of safety. The first point which they emphasize is the advantage of controlling the injection under the roentgenoscope. This enables one to judge just how much pressure is needed and to stop the injection immediately if any fluid enters the peritoneal cavity. Another clever point which they mention is their method of controlling the pressure of the injection. By simply interposing a small rubber bulb between the thumb and the syringe piston and connecting this bulb to a manometer, it is possible to read the pressure directly. By having a radium dial on the manometer it can be seen in the dark roentgenoscopic room and so the pressure is at all times under complete control. The elasticity of the rubber bulb introduces a small error in reading but this is constant and unimportant. They use pressures varying from 80 to 200 mm. of mercury.

**Results of Surgical Treatment of Uterine Fibroids.**—JINKINS (*Texas State J. Med.*, 1928, 23, 735) reports the results obtained in the surgical treatment of uterine fibroids at the John Sealy Hospital at Galveston, Texas. In the period 1920–1926 there were 245 uncomplicated cases treated with 2 deaths, a mortality of 0.8 per cent. During this same period there were 363 complicated cases treated with 17 deaths or 4.6 per cent mortality. There were 518 supravaginal hysterectomies performed with 15 deaths (2.9 per cent mortality), 37 myomectomies with 3 deaths (8.1 per cent mortality) and 42 complete hysterectomies with 1 death (2.4 per cent mortality). These statistics are in accord with our own experience in that they definitely show that the mortality in

the treatment of the uncomplicated cases is materially lower than that of the cases which are complicated by adnexal disease. Jinkins believes however, that the mortality in the complicated group will not be so high in the future because he will not operate upon cases of pelvic inflammatory disease complicating myoma until the infection has been quiescent two weeks or more. At present these patients are frequently discharged from the hospital when they are strong enough and instructed to return in from two to six months for operation. This is a very wise plan to follow if the urgency of the symptoms due to the myoma will allow the delay and undoubtedly will reduce not only the mortality but the morbidity as well. The mortality of 8 per cent for the myomectomy cases seems somewhat high as compared with the mortality from the other types of operation.

**Treatment of Pelvic Inflammatory Disease.**—For several years past the conservative management of pelvic inflammatory disease has been stressed in the literature throughout this country and we have always been glad to emphasize this fact because our own opinion, based on past experience, is in complete accord with such procedure. It is of interest, therefore, to note that the idea of conservative management is becoming popular in Germany, as evidenced by the report of CONRAD (*Zentralbl. f. Gynäk.*, 1928, 52, 2877) from the Rudolph Virchow Hospital in Berlin. During the past five years there were 2825 cases of pelvic inflammatory disease treated on his service, and of these only 373, or 13.2 per cent were operated upon with a mortality of 2.9 per cent. Of the cases operated upon, total hysterectomy was performed only 4 times with 1 death, supravaginal hysterectomy was employed in 71 cases with 5 deaths, while in 298 cases a conservative operation was performed with only 5 deaths. In the conservative group as much ovarian tissue as possible was saved in order to perpetuate menstruation in the young women who constituted the large part of the series. If the radical operation had to be performed, then ovarian transplantation was performed whenever possible, using ovarian tissue from another patient if necessary. These excellent results in such a large series of cases demonstrate the possibilities of conservatism beyond any reasonable doubt.

## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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**Otologic and Other Manifestations of a Diet Deficient in Vitamins. Animal Experimentation.**—The knowledge that various pathologic conditions result from certain discrepancies in food has initiated an era of extensive study of the factors involved. The recent wave of enthusiasm concerning the caloric values of food has been supplanted

to a degree by the present interest in vitamin content. Because of the changes in bone in rickets, suggesting a possible connection between vitamin deficiency and deafness, BARLOW (*Laryngoscope*, 1927, 37, 640) conducted a series of experiments which "definitely established that deficiency of vitamin D in itself was not a factor in the production of loss of hearing." In the present report, relative to the possibility of the other vitamins and their relation to disturbances of the ear, nose and throat, BARLOW (*Arch. Otolaryngol.*, 1928, 8, 629) continued his investigations along similar lines, by examining sections from the bony capsule of rats fed on a diet deficient in fat-soluble vitamin A, and vitamin B. It was found that vitamins A and B were not factors in bony changes in the internal ear and a diet deficient in them was not a predisposing cause of deafness. An absence of vitamin A is marked by such changes in the mucosa of the respiratory tract as edema, small-cell infiltration and desquamation, accompanied by rhinitis. These respiratory lesions might be considered as a possible factor in the production of alterations in the soft tissue of the middle ear, which might become permanent.

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**Vasomotor Affections of the Internal Ear.**—Vasomotor disturbances may be considered as among the most pathognomonic and the most important in affections of the internal ear. These vasomotor troubles depend directly on the sympathetic system. After experimentation relative to the action of the sympathetic (pericarotid sympathectomy and injections of vasomotor drugs), as well as to the effect of circulatory disturbances (arterial compression and peripheral vasodilatation), on the labyrinth, PORTMANN (*J. Laryngol., and Otol.* 1928, 43, 860) discusses some of the vasomotor affections of the internal ear. He calls attention to Lermoyez's syndrome, originally interpreted as angiospasm of the anterior labyrinth and encountered in a patient with Raynaud's disease, whereby the slow stenosis of the internal auditory artery caused deafness which was relieved by the sudden cessation of the spasm and the consequent rush of blood, which, in turn, gave rise to tinnitus and vertigo. In commenting upon Lermoyez's syndrome as "vertigo that makes one hear," Portmann contrasts it with Ménière's disease, in which the phenomena are the same but appear in the reverse order, namely, good hearing; sudden vertigo, sudden deafness and slow recovery. Following a thorough résumé of our knowledge concerning the pathogeny of Ménière's disease, the author states that "whatever may be the internal mechanism of production of vertigo of aural origin, it seems to be, in Ménière's disease, closely connected with the vasomotor phenomena, and hence with the sympathetic equilibrium." In the angiospasmic syndrome of the labyrinth are included: tinnitus, deafness, vestibular hyperexcitability and sympathetic hypertonia. He concludes that "the most important causes susceptible of acting on this regulating apparatus are undoubtedly the action of the nervous system and the action of the endocrine glands, above all the hormone of the suprarenal gland—adrenalin;" and asks the question: "Is the hypertonicity of the arterial coat in the spasm due to the hyperactivity of the sympathetic or to a hyperfunction of the suprarenal?"



**Bone Pathology and its Relation to the Problem of Otosclerosis.**—Applying the idea, that in general the contested questions of bone pathology are also those of normal bone histology, to the pathology of the bony capsule of the inner ear and consequently to the problem of otosclerosis, and believing that research into the etiology of otosclerosis requires a knowledge of the final construction and development of the bony capsule, WEBER (*Ann. Otol. Rhinol. Laryngol.*, 1928, 37, 1232) states that as far as is known this development, in all probability, follows the general principles of bone formation. After an extensive review of the general principles of normal and abnormal bone formation and of the normal growth of the osseous capsule of the labyrinth, the author follows Lange in indicating that in the focal lesion of otosclerosis one may note an intermingling of fibrous and lamellar bone and an absence of interglobular spaces. Weber says that the primary process of the disease is, in all probability, one of resorption, which proceeds slowly toward the periosteal bone. However, he remarks that since otosclerosis is not merely a problem of pathology, the solution of the problem, as Fraser and Pritchett have repeatedly pointed out, necessitates the close coöperation of all the specialists concerned.

Interested in the same subject,—“**The Pathology of Otosclerosis.**” —MAYER (*J. Laryngol. and Otol.*, 1928, 43, 843) concludes that areas of otosclerosis are to be regarded as hyperplasias—a view based not only on the histologic appearance of the foci, but also on their multiplicity, their typical and symmetrical localization, the presence of tiny islands of atypical tissue (constituting points of origin in these areas), the condition of hyperplasia of the temporal bone generally, the appearance clinically of congenital features, the coincidence with blue sclerotics and osteopsathyrosis, Paget’s disease, and neurofibroma of N. VIII, and last, the hereditary factor.

**Retropharyngeal Abscess.**—BARLOW (*Ann. Otol., Rhinol. and Laryngol.*, 1929, 38, 205) in commenting upon the relative frequency of retropharyngeal abscess in early childhood, quotes Babbitt as stating that while the associated pathologic condition offers little complexity, the failure to recognize its existence not uncommonly leads to serious and even fatal consequences. Believing that retropharyngeal abscess is most likely due to extension or invasion from upper respiratory infection, he recognizes suppurative retropharyngeal lymphadenitis from sinusitis and tonsillitis as a potential etiologic factor. The symptoms are those of pharyngeal or postnasal obstruction—such as dyspnea, dysphagia, pain in throat, earache, and a brassy quality to the voice or cry. Objectively, the patients look ill, breathe with their mouths open and often have a unilateral cervical adenitis. The pharyngeal wall usually is swollen and bulging. Palpation is a most valuable diagnostic procedure. The treatment is surgical, and consists of a longitudinal incision—great care being exercised to prevent aspiration of the evacuated pus.

**Laryngeal Cancer: Early Diagnosis and Treatment.**—In a comprehensive contribution concerning the symptoms, clinical findings, diag-

nosis, prognosis and treatment of laryngeal cancer, MACKENTY (*Arch. Otolaryngol.*, 1929, 9, 237) states that malignant disease of the larynx constitutes 5 per cent of all (primary) malignant tumors; that 98 per cent are carcinomata and 2 per cent are sarcomata; and that of the carcinomata, 96 per cent are squamous cell and extremely malignant. From a surgical and prognostic standpoint, the exact location and extent of the cancer (extrinsic, intrinsic or borderline intrinsic) are of great importance. In 90 per cent of the cases, intrinsic cancer gives immediate notice of its presence in a hoarse or altered voice. "In no other situation in the body does cancer give such early or such easily recognizable warning of its presence." The data for differentiating the triad—cancer, syphilis and tuberculosis—are detailed. The treatment is surgical. "Surgical measures, applied early, give better results in cancer of the larynx than in cancer in any other part of the body." In the author's experience, "radium has been an utter failure for treatment in cases of squamous-cell laryngeal cancer (*i. e.*, in 96 per cent of laryngeal cancers). Its false promise is luring thousands beyond the aid of surgical procedures. In over 700 cases studied, 80 per cent of the cancers were intrinsic and curable in their inception; and 230 patients were treated surgically with a surgical death rate of under 3 per cent. Recurrences in incipient intrinsic cancer occurred in 3 per cent of the patients after laryngectomy and in 35 per cent after thyrotomy. In extrinsic cancer, recurrences occurred in almost 100 per cent." In conclusion, Mackenty says: "If the public mind could be oriented on one fact—that progressive hoarseness is a danger signal—and if the medical profession would urge a thorough and competent investigation of this danger signal; if the entire truth were told about radium, and if the laryngologist would heed the dictates of general surgical measures in the treatment of persons with cancer, *i. e.*, radical removal, laryngologists would be doing their honest best with their allotted 5 per cent share of patients with this dire disease and would eradicate to a large extent the unspeakable misery attendant on uncontrolled laryngeal cancer."

**Response of Vestibular Apparatus to Drugs.**—"Otolaryngologists have long felt more or less helpless in relieving vertigo originating in the vestibular organ. A considerable number of drugs have been employed by various men at various times. None have been effective to any satisfactory degree." Regarding the vestibular nerve as one of special sense, ROSS and FISH (*Ann. Otol., Rhinol. and Laryngol.*, 1929, 38, 175) conducted a series of tests of the action of certain drugs on the canine vestibular function—in order to determine the effects of the drugs on the response of the vestibular apparatus to stimulation, as elicited by rotating the animal at a constant rate of about thirty-five turns per minute for fifteen seconds. It was found that of the six drugs employed, three of them—sodium nitrite, cocain and pilocarpin—decreased the response; and that the other three—epinephrin, nicotin and atropin—had no effect. From the known action of the various drugs used and from the results obtained under the conditions of the experiments, the authors believe: that the drugs decreasing the response to vestibular stimulation did so, not as a result of any specific effect, but by reason of the general depression due to the prostrating doses of

the drugs; and that neither the thoracolumbar sympathetic ganglions or the craniosacral sympathetic system are involved in the nystagmus response to vestibular stimulation.

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**Laryngo-rhinology and General Medicine.**—In the Semon Lecture of 1928, HAJEK (*J. Laryngol. and Otol.*, 1929, 44, 3 and *Laryngoscope*, 1929, 39, 75) after reviewing the development of laryngo-rhinology, discusses the relative merits of such diagnostic procedures as histologic, serologic and radiologic examinations and illustrates various points by means of personal clinical experiences. Following a consideration of the very important connections between laryngo-rhinology and internal medicine and surgery, the author concludes that: "The specialty of laryngo-rhinology is only conceivable as a useful department in the whole general field of medicine. It will not suffice that young physicians should dedicate themselves to laryngo-rhinology immediately or soon after the completion of their studies. Particularly impracticable is this method for those who are determined to enter upon an academic career and to busy themselves as teachers in the province of medicine. Post-graduate education lasting for years in most of the departments of general medicine and surgery, and a practical knowledge of histology, hematology and roentgenology, are absolutely requisite as a basis.

"We must first be good doctors; only then can we practically and scientifically further develop a specialty, laryngo-rhinology included. In no other way, for a house is not built from the gables toward the foundation stone, but reversed, and the tree bears fruit only when it is fully developed.

"Let us, therefore, cherish and protect most carefully the tree of general medicine, so that the fruit of the special department may grow so much the ripper and more perfect."

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**Otitis Media and Allergy.**—LEWIS (*Ann. Otol., Rhinol. and Laryngol.* 1929, 38, 185) states that he has encountered 6 cases of acute otitis media which strongly suggested an allergic basis of the inflammatory reaction and presents the clinical data of the 2 cases giving a history of allergic manifestations in their progenitors. In discussing allergy in general, he says that "abnormal tissue reactions" may be subdivided into: (1) allergy—always inherited and of protein etiology; (2) anaphylaxis—always acquired and of protein etiology; and (3) altered reactivity—always acquired and of nonprotein etiology. Attention is directed to the altering influences of adrenalin, iodine and ephedrin on these "abnormal tissue reactions;" and from the knowledge of the action of adrenalin and iodine it is suggested that the endocrine system may participate in the alterations of allergic reactions. Lewis concludes that "there are certain characteristics of so-called 'acute serous' otitis media which suggest the absence of infectious etiology; and even more strongly suggest allergic etiology." Furthermore, he thinks that many instances of acute otitis media may be, originally, the expression of the allergic state, and may be infected, subsequently by the invasion of bacteria into the tympanic cavity.

**RADIOLOGY**

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**Roentgenologic Diagnosis of Diseases Affecting the Distal Half of the Colon.**—Most organic diseases of the colon, when advanced, says MOORE (*J. Am. Med. Assn.*, 1928, 91, 1094) give rise to pronounced and diagnostic roentgenologic signs. Early lesions are less easily discovered, and more difficult to distinguish from each other than equivalent lesions of the stomach. Among the roentgenologically demonstrable diseases that affect the distal portion of the colon, from the splenic flexure to the rectum, the three most common are diverticulitis, cancer, and ulcerative colitis. Of much less frequent occurrence are benign tumors, cicatricial strictures, tuberculosis and Hirschsprung's disease.

Diverticula occur in every part of the alimentary canal but are found most frequently in the colon, especially in its distal half. They are found in approximately 5 per cent of all patients examined with the Roentgen ray. In most cases the sacculations are few in number, symptomless and without clinical significance. Often, especially in the sigmoid, they are numerous and become inflamed—diverticulitis and peridiverticulitis. The inflammatory thickening produces a corresponding narrowing of the barium-filled lumen of the bowel. The margin of the narrowed lumen is likely to be serrated, and unless a few diverticula, which appear as round or oval shadows, are manifest, the appearance may be difficult to distinguish from that of colonic spasm, cancer or adhesions.

Cancer is rather common in the distal colon. Its principal manifestations are a narrowing, deforming defect in the barium shadow, with or without obstruction to the enema. Scirrhus cancer often encircles the bowel, producing the stenotic, so-called napkin-ring form, and is easily recognized. Medullary cancers grow rapidly, ulcerate deeply and deform the lumen grossly. At the site of the defect, a mass can usually be felt.

Chronic ulcerative colitis usually begins in the distal part of the bowel and progresses upward. When the disease is well advanced the affected bowel, when filled with the barium enema, is narrow, devoid of haustra, smooth and pipelike or deeply constricted at intervals, so as to resemble a string of sausage. Frequently the colon is contracted longitudinally, causing the splenic flexure to be drawn downward.

**Bone Diseases.**—BELDEN (*Radiology*, 1928, 11, 281) feels that osteitis deformans and osteitis fibrosa are the same disease, but that osteitis fibrosa is the manifestation of Paget's disease in the young and that

osteitis deformans is the reaction of the bones in the adult past middle life. Osteomalacia can perhaps be added to the group. Osteitis deformans affects chiefly the bones of the leg, the vertebræ and skull, although almost any bone may be attacked. Roentgenologically, the bone becomes dense, widened and, if a long bone, considerably bowed; the vertebral column is almost always involved; and kyphosis develops in the dorsal and lower cervical regions; enlargement of the skull usually occurs at some stage of the disease, and is produced by an enormous deposit of bone on the outside of the cranium, without endocranial thickening; the pelvis may be broadened, the ribs thickened and the chest deformed. Paget's disease is a strong predisposing cause toward the development of sarcoma of bone which has occurred in nearly 10 per cent of the recorded cases. Osteitis fibrosa cystica consists in the formation of new connective tissue which may soften and give rise to cysts. It is considered by Bloodgood and others to be an inflammatory condition, a low-grade form of osteomyelitis. On the other hand, there is evidence that it is an obscure disorder of calcium metabolism and ossification. It is a disease of the young, most cases occurring between the ages of ten and twenty years. Bones affected most commonly are the humerus, the femur and tibia. Bowing, angular deformities and fractures may result. In the roentgenogram the cysts produce a striking picture; the clear area is often continued down the shaft as a pointed extension, whereas in other bone cysts, such as those which occur in giant-cell tumors, the lower limit is rounded. However, the disease may be complicated by the development of giant-cell tumor. Osteomalacia is of extreme rarity in North America. It seems to be a deficiency disease due to the lack of some vitamin in the food plus chronic infection. The disease is one of middle life and is almost confined to pregnant or parous women. Many bones may be affected, but those exhibiting most the effect of the disease are the lumbar vertebræ, the pelvis and the bones of the leg. The vertebræ are compressed, the pelvis deformed, the bones of the leg are bowed outward and forward and general rarefaction of the bone is obvious in the roentgenogram.

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**Fractures from an Operative Viewpoint.**—HENDERSON (*Radiology*, 1929, 12, 214) lists the recent closed fractures most satisfactorily treated at the Mayo Clinic by some form of open method, as follows: In the lower extremities—astragalus, if there is marked displacement; Pott's fracture, if the malleolus is broken off high and well into the articular surface of the tibia; refractory fractures of the ankle with spiral fracture of the fibula, broken internal malleolus, etc.; oblique breaks of the lower third of the tibia and fibula; patella; shaft of the femur in the adult, particularly in the lower third with posterior displacement of the lower fragment; fracture dislocations of hip; slipped epiphysis in the upper end of the femur in children (should be operated on early). In the upper extremities—overriding fractures of metacarpals; badly comminuted fractures of scaphoid; most fractures of the shaft of both ulna and radius; lower third of radius (other than typical Colles); head of radius; olecranon process; fracture or epiphyseal separation of the lower end of the humerus in children; particularly if the lower fragment is displaced anteriorly; surgical neck of humerus with overriding; fracture dislocations of the head of the humerus. Henderson

goes on to say that the open method is being used more and more, but it should be employed only by those who are properly qualified and in proper surroundings. The use of the open method as a routine is not advocated. Whenever possible the conservative method should be used.

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**Roentgen Findings in Neuroblastoma.**—Two cases of neuroblastoma are reported by HENLE (*Am. J. Roentgenol. and Rad. Therap.*, 1928, 20, 414). Neuroblastomas, formerly considered sarcomas or gliomas, arise from the formative cells of the sympathetic nervous system. Their most frequent situation is the adrenal but they may arise in the intestines, paravertebral ganglia or uterus. Metastasis may occur to the liver or to the orbit, skull and long bones. The disease occurs mostly in infants and young children, but adults may be affected. In Henle's two cases, one with the primary tumor in the adrenal, the other in the paravertebral ganglia, metastasis occurred to bones and soft parts and the cranial roentgenograms had several striking points in common. In each the coronal suture was gaping widely, probably incident to intracranial pressure from metastasis to the brain. The cranial bones had a porous appearance, due to generalized pin-point areas of rarefaction; seen sagittally the rarefactions seemed to be arranged radially. Henle's second case illustrates a point previously made that neuroblastoma of the adrenal is associated with involvement of the orbit of the same side; if both orbits are affected the more extensive involvement is found on the same side as the primary tumor.

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**Roentgenologic Diagnosis of Ureteral Stricture.**—Although urography offers the best method of determining the existence of ureteral stricture, BRAASCH (*Radiology*, 1929, 12, 183) observes that there are many factors which lessen the accuracy of this procedure. This is particularly true when the ureteral dilatation above the obstruction is moderate or confined to the area immediately adjacent to the stenosis. To add to the confusion, the outline of the normal ureter varies considerably. While it is well known that in most normal ureters there are three areas of relative narrowing, this is not constant and the caliber varies in different portions. Added to this is the difficulty of uniform distention. Overdistention in one part with incomplete filling adjacent to it might easily give the impression of dilatation. Return flow alongside the catheter is difficult to overcome, and as a result areas of apparent constriction may disappear when a second roentgenogram is made with more complete distention. With so many factors involved, an unqualified diagnosis may be impossible.

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**Hysterosalpingography and the Diagnosis of Ectopic Pregnancy.**—RUCKER and WHITEHEAD (*Am. J. Roentgenol. and Rad. Therap.*, 1928, 20, 431) report a case of relatively early, ruptured tubal pregnancy in which roentgenography after the injection of lipiodol exhibited an elongated cervix and an enlarged uterine cavity which was irregular of contour, evidently because of adherent blood clots. The right tube filled well, but no oil entered the affected left tube. The observation tends to bear out the statements of Schneider and Eisler who have said that the actual visualizing of a tubal pregnancy by injection of lipiodol

is too much to hope for, but that hysterosalpingography gives valuable indirect evidence. First, the uterus is likely to show a rounded or globular form due to a pregnancy atony, without the filling defect that would indicate an intrauterine ovum. Second, the tube should exhibit one of several forms of total or partial occlusion. In other words, a globular uterine cavity with one patent tube and the other occluded or defectively filled is strongly suggestive of tubal pregnancy.

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**Bone Changes in Leprosy.**—Bone changes are usually marked in both types of leprosy whether of the skin or nerves, writes RALPH HOPKINS (*Radiology*, 1928, 11, 470). The most marked osseous change takes place in the phalanges of the extremities and the nasal septum, while the bones of the trunk and the long bones of the legs and arms are untouched. The actual loss of bones causes a mutilation of the hands and feet which is so characteristic of leprosy. There may be absorption of bone without any evidence whatsoever of inflammation or suppuration of the overlying tissues. Bone loss is followed by retraction of the soft tissues, the tips of the finger nails often projecting from the phalanges when the digit has disappeared. The absorption of the nasal septum is followed by the sinking in of the soft parts of the nose. This process of bone absorption is usually a very slow one. Ten, twenty or thirty years may elapse while the digits are gradually shortening. When suppuration occurs, of course, it is much more rapid.

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**Roentgenology of the Urinary Bladder.**—JUHL (*Radiol. Rev.*, 1929, 51, 1) in discussing the roentgenologic demonstration of calculi in the bladder, observes that only a positive finding is decisive, while a negative finding does not exclude the presence of stone because small uric stones may be invisible on the film. It is an error to regard every opacity in the area of the bladder as a stone. Shadows resembling those of stones may be produced by scybala, intestinal calculi, foreign bodies in the intestine or bladder, calcification in the walls of the pelvic arteries, phleboliths in the pelvic veins, calcified retroperitoneal glands, foreign bodies in the vagina and uterus, calcified uterine myomas, normal or extrauterine pregnancy, dermoid cysts, and calcified pelvic exudates. To establish the differential diagnosis between vesical calculi and the foregoing simulants is often a difficult task for the roentgenologist and only the keenest observation and best judgment can clear up the diagnosis.

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**Obscure Kidney Lesions.**—Several cases of nephroptosis with kinking of the ureter, renal calculi and renal tumor, all with obscure symptoms, are reported by BOWMAN and GOIN (*Radiology*, 1929, 12, 188). They suggest: (1) that in all cases with unexplained abdominal pain a complete genitourinary examination including roentgenograms before and after injecting the kidney and ureter, be made, and (2) that, when indicated, the examination should include pyelograms with the patient in an upright position. Only by the latter method were the cases of renal ptosis with ureteral kinking which they report demonstrable.

## NEUROLOGY AND PSYCHIATRY

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**Some Laboratory Findings in Epilepsy.**—PATTERSON (*The Psychiatric Quarterly*, 1929, 3, 82) states that albumin and casts appear in the urine of epileptics at any time within the first two hours after an attack and may not disappear until the fourth day. As the seizures continue chronic changes in the kidney may be induced. This condition of albumin and casts in the urine is found in about 20 per cent of epileptics. As to blood pictures, he finds that many patients exhibit a moderate to high leukocytosis during the interparoxysmal period as well as during the attack without any discoverable foci of infection. A small number show a persistent leukopenia. Leukocytosis is generally present and the large lymphocytes tend to appear more numerous than normally. Eosinophilia is usually present. Considerable numbers of degenerated white cells may be present. Secondary anemia was not common in cases studied by him. The blood platelets seemed to disintegrate with great rapidity and the bleeding time is prolonged and coagulation time delayed. He states that during convulsions nonprotein nitrogen, uric acid, creatinin and serum protein show an increase of varying degree. He cautions against accepting even quite high values in severe attacks as symptoms of uremia. He finds the blood-sugar content generally to be low, whereas the blood calcium is generally not decreased. The spinal-fluid pressure in 50 cases, he found to be in the upper borderline of the normal and much influenced by external mechanical factors. Spinal-cell count, albumin, globulin, chlorid and urea contents were all within normal limits. The absolute sugar value of the spinal fluid was low. Protein sensitization was found in 37 to 58.8 per cent of patients tested, as compared with an incidence of 8 per cent among nonepileptic controls. Syphilis, as determined by the Wassermann test and clinically, he found in only 8 per cent of admissions to Craig Colony and this has fallen to 5 per cent in the last eight years. Autopsy, he states, frequently fails to disclose any constant gross abnormality in the central nervous system. The most frequent pathological defects encountered are microcephaly, hemiatrophy, chronic internal hydrocephalus, focal cerebral softening and brain tumors. He states that such findings cannot be considered as pathognomonic of epilepsy as they also occur in the feeble-minded and the insane.

**Tryparsamid Treatment of General Paralysis.**—KIRBY and HINSIE (*The Psychiatric Quarterly*, 1929, 3, 68) present a review of 69 cases five years after the beginning of treatment with tryparsamid. They



find remissions 28 per cent; improved, 26 per cent; unimproved, 12 per cent; dead, 34 per cent. Two of the original 69 cases could not be located but had previously been regarded as having attained a complete remission. Since the original report on this group in 1926, they have noted few changes in the status of the patients. "It is our impression that, after a patient has undergone tryparsamid treatment to the extent of 40 or 50 injections (3 gm. per dose), as a rule the maximum clinical benefits are reached. Patients may continue to improve thereafter but it is not at all certain that further progress, which is usually slight, has much to do with tryparsamid itself." The greatest variation occurred in the group termed unimproved which changed from 20 to 12 per cent. They consider these results similar to those found in patients who have received malarial therapy. They believe that even in the unimproved group an arrest of the disease process has taken place. The serologic changes are not parallel with the clinical changes. Certain patients show a progressive change from strongly positive serology to negative serology. Others show a continuation of the positive serology even though the clinical improvement is marked and some cases show a tendency to become negative at some period during the treatment and later show a recurrence of strongly positive serology while clinically the improvement continues.

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**Personality Changes in Children following Cerebral Trauma.**—KASANIN (*J. Nerv. and Ment. Dis.*, 1929, 69, 385) finds 10 per cent of 120 cases diagnosed as psychopathic personalities to have had serious cerebral injury. Only 2 cases in a control group of 120 selected children had had very serious cerebral injury. He considers the personality changes found following brain trauma to be similar to those followed in epidemic encephalitis. Extreme emotional instability, temper tantrums, egocentricity and inability to follow a definite goal in life are common but he considers the prognosis to be better in the posttraumatic group. He recommends that cases which present difficult problems of social behavior be studied very carefully with reference to early encephalitis or brain injury. He would direct attention especially to such situations as hard labor with application of high forceps. As diagnostic points he recommends a systematic, thorough neurological examination and attention to such phenomena as inability to stand heat or shut-in places. These symptoms were frequently found in the cases studied. He also recommends encephalography by lumbar puncture for the purpose of demonstrating whether there has been any atrophy of the brain or any structural abnormalities. As to treatment he recommends environmental change and psychotherapy. He states that one should avoid overlong experimentation in attempts at social adjustment as these cases are best cared for by special training in correctional institutions under intelligent supervision. As a prophylactic measure he recommends removal of the child into the country, away from city excitement and city stimulation, shortly after the accident.

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**A Modification of the Babinski Phenomenon.**—FOXÉ (*J. Nerv. and Ment. Dis.*, 1929, 69, 414) presents an interesting and easily performed modification of the Babinski reaction. "The right hand is used in studying the right foot and the left hand in studying the left foot. The

foot is clasped from the lateral aspect so that the last four fingers approximately touch the midplantar region, while the thumb is placed on the anterior surface of the foot upon or slightly lateral and distal to the metatarsocuneiform articulation of the great toe. Gradually increasing pressure is made on the plantar and anterior surfaces of the foot after which the pressure is suddenly released. Occasionally in instances where the Babinski sign is unusually prominent a dorsal extension of the great toe may occur upon the application of pressure, but this does not interfere with a second response that occurs when the pressure is removed." He finds this phenomenon present in cases of disease of the brain and cord associated with hyperreflexia and hyporeflexia. It has been found where other modifications have been absent and has been suggestive when the Babinski sign has been suggestive.

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**The Influence of General Paralysis on the Family.**—HINSIE (*The Psychiatric Quarterly*, 1929, 3, 90) finds in a series of 86 patients with general paralysis that the Wassermann reaction was positive in 19 of the marital partners. Eight of the 19 individuals show clinical and serological evidence of general paralysis. Of 42 families in which one or both parents were patients with general paralysis, 49 living children were examined who were born while the parent or parents were syphilitic. Seven of these children were found to have inherited syphilis. He considers it highly improbable that a special neurotropic strain of *Spirocheta pallida* can be said to exist. An interesting observation was that of syphilis occurring in one of a pair of identical twins while the other twin was negative. He concludes that every member of a family in which syphilis appears in one or more individuals should be carefully examined for the same infection.

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**Basal Metabolism in Schizophrenia.**—HOSKINS and FRANCIS H. SLEEPER (*Arch. Neurol. and Psychiat.*, 1920, 21, 887) present 80 cases of schizophrenia in which the basal metabolic rate was studied. Of these 43, or 56 per cent fell below the conventional 90 per cent which marks the lower level of normality. The remaining group all fell within the normal range. The extremes of the basal metabolic rate determinations were 71 per cent and 106 per cent. The low findings were fairly uniformly scattered between the various diagnostic groups. The mean value for the 80 cases was 89.1 per cent. The pulse rate was also low, ranging between 42 and 86, with a mean value of 61.1. Of a total of 286 cases which the authors collected from the literature 47.9 had basal rates below 90 per cent. They conclude that the basal metabolic rate in persons with dementia precox average characteristically more than 10 per cent below normal.

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**Encephalitic Diaphragmatic Spasm Treated by Phrenicotomy.**—SPEIRS (*J. Nerv. and Ment. Dis.*, 1929, 69, 407) presents a case of respiratory tic consisting essentially of a spasm of the diaphragm together with a spasm of other muscles of respiration. Bilateral phrenicotomy was performed with great benefit to the patient although he continues to show a persistence of the tic, especially due to the disturbed innervation of the anterior neck and chest muscles.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**Osteogenic Sarcoma in Dial Painters Using Luminous Paint.**—MARTLAND and HUMPHRIES (*Arch. Path.*, 1929, 7, 406) report the occurrence of 2 cases of osteogenic sarcoma presenting themselves in a series of 15 deaths among painters of luminous watch dials due to radium-mesothorium poisoning. The greater part of the radioactive material gained access to the body through ingestion. Some of it was absorbed, distributed by the blood stream, phagocytosed by the reticuloendothelial system, and ultimately stored, particularly in the bones, as insoluble sulphates. Irradiation, more especially by the alpha rays of radium and mesothorium, the former exhibiting an initial velocity of one-twentieth to one-twelfth that of light, subjected the surrounding tissues, osseous and hemopoietic, to a constant terrific bombardment by the ejected particles. The effects of these substances, exerted over a period of years led to extreme degrees of anemia, aplastic or feebly regenerative in type, to irradiation osteitis of bone to which were frequently added the effects of the osteomyelitis, of secondary infection and upon occasions to neoplasm of bone. In the case described the patient eight years after exposure showed roentgenologic evidence of an irradiation osteitis in the scaphoid bone of the right foot, in the right humerus, and in the right scapula. A year later roentgenograms for the first time showed a sarcoma of the right scapula, arising from its anterior and superior portions. Three months later, at autopsy, this diagnosis was confirmed and the tumor was found involving the whole anterior and upper part of the bone with infiltration into the supraspinous and infraspinous muscles. Visceral metastases were not found. Microscopically, the sections of the tumor were typical of osteogenic sarcoma with new formation of bone and cartilage, while the bone marrow showed a regenerative leukopenic anemia of the megaloblastic type. It was possible to demonstrate radioactivity in the bones of this individual by photographic and scintillation methods and through the aid of the alpha electroscope. It was estimated that the entire skeleton contained 50 micrograms of radioactive substances. Although the alpha rays of these radioactive bodies do not penetrate the skin for a greater depth than 1 mm., the beta and gamma rays (5 per cent of emanating particles) do possess the power of penetration. A number of cases have been reported in the literature in which sarcoma has followed radium treatment. The attention of radiotherapeutists is called to the possibility of the production of malignant growths by excessive irradiation.

**Leukochloroma in the Common Fowl.**—MATHEWS (*Arch. Path.*, 1929, 7, 442) has studied 37 myeloid neoplasms occurring in the fowl for which he suggests the name of leukochloroma because of their similarity to the chloroma or chloroleukosarcoma of man. The avian disease is not uncommon, being found in the author's experience in somewhat over 0.8 per cent of 3938 autopsies. Since 30 per cent of the flocks concerned in this investigation had a common ancestry, an hereditary factor in connection with the occurrence of the disease is suggested. The disease occurs sporadically in birds under one year of age, but it may become enzoötic. The characteristics which it shares in common with the chloroma of man consist in tumorous development resulting in a rarefaction of the sternum, the ribs, and the spinal column with early metastases, especially affecting the liver but leaving no part of the body exempt, and accompanied by an enlargement of the spleen and lymph nodes, with a leukemic state of the blood. In both, the disease occurs usually in early life and runs a rapid fatal course. The tumor in the fowl lacks the green coloration sometimes observed in man, and apparently the predilection for the bones of the cranium with the attendant exophthalmos. The leukochloroma differs from the lymphocytoma of fowls in occurring in young birds, in its rarefaction of bone, its chalky-white appearance in the gross, in the nature of its typical cell which resembles the myelocyte and in its association with myelogenous leukemia. The lymphocytoma is a gray tumor, occurring in birds of all ages, not producing erosion of bone, composed of a lymphocytic type of cell and associated with a lymphatic leukemia. Young fowls inoculated with tumor material by various routes, subcutaneous, intraperitoneal and subperiosteal failed to reproduce the disease. Grossly the leukochloroma presented infiltrations of the liver, kidney, ovary, spleen, intestine, heart and vertebrae, the latter with pressure upon the spinal cord and resulting transverse myelitis. Microscopically the tumor was extremely cellular. The cells were spherical, unless distorted by pressure, about equal in size to the mature avian myelocyte and supported by a scanty reticulum with a rather abundant blood supply. Each cell possessed an eccentrically located, round or oval nucleus, occupying about one-half of the cellular space. Mitotic figures were numerous. The cytoplasm was of definite outline and filled with numerous spindle-shaped granules which took a brilliant eosin stain.

**So-called Infectious Sarcoma of the Dog in an Unusual Anatomic Situation.**—FELDMAN (*Am. J. Path.*, 1929, 5, 183) reviews the literature of a peculiar tumor occurring in dogs which presents on the one hand the clinical behavior of an infectious granuloma and on the other the invasive properties and morphologic appearances of a rapidly growing malignant neoplasm. The author describes a case of this so-called infectious sarcoma arising in a young dog in which two tumors which were morphologically indistinguishable from transmissible sarcoma of the genitals appeared respectively in the orbital cavity and under the skin of the frontal region. The genitals were not affected. The tumors were removed successfully and the animal continued in good health. Other tissues were not examined. Neither the origin of the tumors nor their relation, one to the other, was determined. The tumors were composed

of rather large irregularly shaped cells, somewhat polyhedral in outline, closely packed together and supported by delicate strands of vascular fibrous tissue. There was no definite stroma. The nuclei, which represented about half of the cellular bulk possessed a large number of coarse chromatin granules. Mitoses were numerous and hyperchromatosis was evident. The cells showed an affinity for the basic stain. A prominent, slightly eccentrically located nucleolus could be seen in the majority of the cells. The tumor cells were markedly invasive. Though they possessed the structural characteristics of the cells of highly malignant neoplasms the tumors did not affect appreciably the animal's health nor did they recur on removal. The author concurs in the opinion of most previous workers in regarding them as true neoplasms and suggests that they may represent a type of lymphoblastoma.

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**Thromboangiitis Obliterans: Experimental Reproduction of Lesions.**—BUERGER (*Arch. Path.*, 1929, 7, 381) has been able to reproduce experimentally the venous lesions of thromboangiitis obliterans in the healthy ligated veins of man by the paravascular implantation of clot removed from the veins of patients suffering from the disease in the stage of acute migratory phlebitis. When after nine to twelve days the experimental lesion in the vein was excised it was possible to demonstrate lesions practically identical with those of acute thromboangiitis obliterans occurring spontaneously; namely, a diffuse polymorphonuclear infiltration of the wall of the vein and a clot in its lumen containing typical miliary giant-cell foci. Similar experiments in two monkeys failed to produce more than a thrombosis without evidence of inflammatory reaction and the intravascular introduction of the suspected infectious material into lumina of ligated veins of humans was without effect.

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**Lymphoepithelioma.**—EWING (*Am. J. Path.*, 1929, 5, 99) reviews the present available data suggesting the recognition of a particular form of epidermoid carcinoma of the nasopharynx, designated by Regaud and Schmincke as lymphoepithelioma. The tumors occur at all ages but are especially frequent in the young and between the thirtieth and sixtieth years, arising from modified epithelium overlying lymphoid tissue in the tonsils, base of tongue and nasopharynx. They grow slowly, remain small locally and are often overlooked, but tend to produce early metastases in the cervical lymph nodes, and later widespread extensions to liver and bone marrow. They are generally fatal. The diagnosis, difficult of distinction from lymphosarcoma on the one hand and transitional-cell carcinoma on the other, must be based on the structure which shows sheets of pale-staining epithelial cells often in syncytia and infiltrated with many lymphocytes, both in the primary tumor and in metastases. The clinical appearance, the course, location and radiosensitivity does not differentiate them from other tumors of the same region. Anaplastic carcinomas may be distinguished by their more rapid course and cellular structure. Since different writers have included under the term lymphoepithelioma various tumors such as transitional-cell carcinoma and Schneiderian carcinoma, the exact definition of the tumor cannot as yet be made.

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**Diphtheria: Its Treatment and Prevention.**—LEE (*Am. J. Pub. Health*, 1928, 18, 1239) states that, although diphtheria antitoxin when given early and in adequate dosage is one of the most efficient of all our specific drugs, yet from thirty-three years' experience in this country it has been but one of the factors in the reduction of diphtheria mortality rates. In most cities and states in which data show diphtheria mortality rates prior to 1895 it is found that the trend of the fall of mortality began from five to twenty years prior to the introduction of antitoxin and has continued ever since unchanged save by the fluctuations due to chance. Scarlet fever mortality, for which we had no specific therapy, has fallen along a trend practically parallel to that of diphtheria. A study of nearly 800 diphtheria deaths in the states of Indiana and New York reveals that even now, after thirty-three years antitoxin to reduce the general diphtheria mortality rates is not due to failure on the part of the drug but rather to our administration of it. Since 1920 there has been a general and marked fall in diphtheria death rates, which is often attributed to the use of toxin antitoxin. If these data for these states or cities are observed over a long period of time it will be found that in most instances the present fall of mortality rates is well within the range of chance deviation from the general trend line, and is entirely insignificant, due, no doubt, in most cases at least, solely to the operation of chance. Although diphtheria antitoxin has apparently played but a minor rôle in the general reduction in diphtheria mortality rates since 1890, this disease is being controlled and may even be eliminated by the intensive use of diphtheria immunization in the child population. To date the writer knows of only six cities where this has been done sufficiently intensively to significantly reduce the diphtheria mortality. There are other cities, no doubt, with similar results which have not come to the writer's notice. In cities where immunization work has been done sufficiently to reduce the mortality rates significantly, it has been accomplished after about one-half of the child population under fifteen years of age has been immunized. Unfortunately, detailed information as to the number of children in specific age groups is often lacking. Such data during the next few years would be invaluable. Since about 60 per cent of the deaths from diphtheria occur under five years of age, and about 35 per

cent between five and ten years of age, or 95 per cent of deaths occur in children under ten years of age it is obvious that in an immunization campaign the work should be concentrated upon the children under ten years of age, and especially upon the preschool children. This last group is the hardest to reach; yet it holds the key position in all immunization work and our efforts will necessarily be relatively unsuccessful as we neglect this group.

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**The Production of Experimental Typhoid Fever in the Guinea Pig with an In Vivo Prepared Toxic Filtrate of *B. Typhosus*.**—In general microorganisms belonging to the so-called endotoxic group do not yield *in vitro* a satisfactory specific toxin. This has greatly interfered with the progress of the study of the true nature and effects of such microorganisms. A definite toxemia is manifestly present in typhoid fever and the toxin produces in the human host a specific pathologic picture. It is not improbable that such a microorganism forms its specific toxin only when invading its natural host, in other words during its function of pathogenesis. A different or more complete biologic process may be involved *in vivo* as contrasted with *in vitro* activity. Again the somatic cells of the invaded host may play some essential rôle in the production of the specific pathogenic toxin. Because of these possibilities of a differential nature of such toxins HARRIS and LARIMORE (*J. Exper. Med.*, 1929, 48, 885) employed the *in vivo* method. They believe that the toxic material obtained through this process closely simulates in its action on the inoculated host the activities of the typhoid toxin as evidenced in the human disease. When the typhoid bacillus is injected into the peritoneal cavity of guinea pigs acute peritonitis and death are produced. When the Berkefeld filtrate of this exudative material is inoculated into normal guinea pigs either subcutaneously, intraperitoneally or intracardially, the character of response obtained on the part of the host is quite at variance with that produced by the inoculation of the living typhoid bacillus. A febrile reaction and marked leukopenia, as a rule, are persistent and are accentuated after each injection, the latter often reaching below 1000 cells per c.mm. There is a loss of weight of a variable extent in all animals and in some the emaciation is extreme. The animals were given four such inoculations and all succumbed in from two to four weeks. The intracardiac route produces death more quickly and the reactions are more clear-cut when this route is employed. At autopsy, a general tumefaction and congestion of the lymphoid structures more especially of the abdominal cavity are found. Peyer's patches and the solitary follicles of the intestinal tract are likewise involved and in some of the patches slight ulceration is noted; occasionally, there occur extreme ulceration and necrosis of the patch. The spleen is enlarged and usually softened. Microscopically, marked endothelial cell proliferation is noted especially in the lymphoid structures and in many instances the phagocytic cells of Mallory are found. These cells include within their cytoplasm elements of the surrounding structures. In the spleen there are present congestion, and hemorrhages with many "shadow" red blood cells. Phagocytosis of the red cells by the endothelial cells is present. In the liver, areas of focal necrosis are found and phagocytic cells are seen.

In the animals inoculated subcutaneously, localized degenerative changes are observed especially in the muscular structures. From these results it can be seen that the reactions and injury of the animal body by the toxic filtrate employed are quite similar to the changes produced by the specific toxin in human typhoid fever. The authors conclude that during the activity of peritonitis produced in the guinea pig by means of *Bacillus typhosus*, there is formed in the exudative material a filtrable toxic moiety which, when inoculated into normal animals of this species, produces certain of the clinical phenomena and a pathological picture simulating that of human typhoid fever.

**Regulating the Production, Handling, and Distribution of Milk.**—WALKER (*U. S. Pub. Health Rep.*, 1928, 43, 2095) points out that regulation of milk is demanded, first, from the public health point of view and, second, to protect the purchaser of the food product against fraud. He notes the frequency with which epidemics have been traced to milk, especially in the case of typhoid fever, scarlet fever, diphtheria, and septic sore throat. The frequency with which diarrheal diseases of young children is due to milk is also noted, as are infections with tuberculosis. The United States Public Health Service requirements state that milk shall contain  $3\frac{1}{4}$  per cent of milk fat and not less than  $8\frac{1}{2}$  per cent of other solids. Types of control are discussed, the first being that in which a license is required for the sale or distribution of milk in a state or municipality; second, it provides for the grading of milk, and third, which is supplementary to the other two, provides for punishment for violation of milk requirements. Specific requirements are discussed as regards adulteration or misbranding, uncleanly conditions in production and handling, and pasteurization. It is noted that the distribution of milk in bulk is usually prohibited.

**Cold Susceptibles Versus Normals: Physique and Past Medical History.**—Some years ago questionnaire studies made by SMILEY (*J. Am. Med. Assn.*, 1924, 82, 540) of large groups of students at Cornell University revealed the fact that in general terms 60 per cent had colds two or three times a year as a rule, 15 per cent had colds never more than once a year, and 25 per cent had colds four or more times a year. Questionnairing of the two extreme groups (the 0-1-a-year group and the 4-or-more-a-year group) revealed no very marked differences between the two groups in regard to smoking, past history of operation on nose and throat, breathing of irritating dust or gas, mouth breathing, hours of sleep, hours of exercise, exposure to drafts, the wearing of woolen underwear, the wearing of galoshes or rubbers, the use of a daily cold bath, the tendency to perspire freely, history of chronic constipation or finally a history of cold-susceptibility in the father or mother. It was concluded that no major factor in the production of colds had been dealt with in the questionnaire though the questions of nose and throat operation, exercise, underwear and heredity merited attention. This past year further comparisons along a somewhat similar line were attempted. It was found (*Am. J. Hyg.*, 1929, 9, 473) that the general physique and the physical defects in cold-susceptible college students are much the same as in normal students



and the cold-susceptible college students present a history of more infectious disease, asthma and hay fever than do normal students. As a result of subsequent studies of the weekly incidence of colds in normal and in cold-susceptible groups throughout a winter, the same author (*Ibid.*, p. 477) believes it probable that the ordinary winter or spring epidemic of colds among college students is a phenomenon almost entirely limited to the cold-susceptible group of students and involving very little the large normal group of students. Any procedure which could succeed in reducing the frequency of colds to two or three times a year in the approximately 25 per cent of persons who now have colds four or more times a year might conceivably entirely eradicate the usual winter or spring epidemics of colds which now cause marked loss of time and result in many fatalities as the result of complicating diseases. With this point in view, MAUGHAN and SMILEY (*Ibid.*, p. 466) conducted experiments with irradiation and found that a ten- to sixteen-minute exposure of the naked body (five to eight minutes front, five to eight minutes back) during the dark months of the year to the rays of an ordinary mercury-vapor lamp once a week at a lamp-table distance of 30 inches in most instances reduced by at least 40 per cent the incidence of colds in cold-susceptible individuals. Since lack of ultraviolet irradiation is only one of several known factors involved in reducing bodily resistance to acute respiratory infection, the control of this factor alone must not be expected to be a complete panacea for the prevention of colds. The results would, however, appear to justify the use of short weekly irradiations with ultraviolet light in certain cases of marked susceptibility to colds where even a 40 per cent decrease in the frequency of colds would be appreciated.

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**Tularæmia Among Meadow Mice (*Microtus Californicus Æstuarinus*) in California.**—PERRY (*Pub. Health Repts.*, 1928, 43, 260) found the infection in two mice sent in from rural California. This constitutes the first record of meadow mice having been infected by this organism, although a large number of other rodents are known to be susceptible. It is suggested that transmission among the mice occurs through mites.

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ORIGINAL ARTICLES.

FATAL INFECTION OF THE INTESTINES WITH *BACILLUS*  
*AËROGENES CAPSULATUS*.\*

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THIS patient apparently had an infection of the intestinal tract with the *Bacillus aërogenes capsulatus*, causing an acute toxemia, from which she died. We have been unable to discover the record of any similar case, and the report seems justified, not only because the case may be unique at this time, but also because it may be possible to draw inferences regarding the nature of some intestinal infections with this organism.

**Case Reports.** S. F., a white female, aged twenty-five years, was admitted on the service of Dr. George M. Laws to the private floor of the Presbyterian Hospital, January 20, 1926. She had soreness in the right lower quadrant of the abdomen for five months, and had lost weight progressively. Her mother had died of kidney disease, following an operation (appendectomy); a sister was insane; another sister and her father were well. The previous history included measles, chickenpox and influenza, numerous sore throats and some abscesses of the ears. Menstruation had

\* This was the last scientific paper prepared by Dr. Sailer, who died December 31, 1928.

been normal. She had noted tenderness in the right lower quadrant for several months, pain in the right sacral region and right hip at irregular intervals, and attacks of pain in the right lower quadrant, ascribed to gas. Micturition was normal; the appetite fair or poor; and there was chronic constipation, with the laxative habit, usually cascara. She thought that she was nervous. She had weighed 104 pounds during the summer of 1925. When admitted she weighed 93 pounds.

She was a thin, excitable young woman. The pupils were rather wide, but otherwise the head was normal. The heart and lungs were normal; the intercostal angle was acute, but the abdomen was otherwise normal; in particular no tenderness was elicited, and no masses were felt; but viscerop-tosis was suspected. The urine contained glucose, confirmed by the phenyl-hydrazin test, but the blood sugar was only 89 mg. per 100 cc. of blood. The clinical diagnosis was chronic appendicitis.

The operation was performed by Dr. Laws, assisted by Dr. Howell, the day after the patient's admission. The appendix was distended and crepitated on palpation, and the walls were congested. There were no adhesions, and no peritoneal exudate. The stump was inverted, and the wound closed without drainage. It was noted that the pelvic organs were normal, and that the appendix contained old hemorrhagic fluid. The following day the patient seemed well; there had been only a slight nausea and vomiting; but on the morning of the 23d a scarlatinal rash was noted, involving the face, neck, shoulders and upper thorax. The temperature was normal. She hiccupped all day, and she vomited occasionally. The abdomen was flat and soft. The throat was not sore. The patient was apathetic, but seemed concerned about the outcome. The morning of the 24th the erythema was deeper and more extensive; the throat was sore, and although the temperature was still normal, the skin was hot and dry. An enema was given, and was followed by the expulsion of a greenish fluid with an intensely offensive odor. She also had some diarrhea, and the movements had the same offensive odor. The patient was weak, the pulse rapid and almost imperceptible. At 2.50 P.M. the blood pressure was 48 systolic; the diastolic pressure was not obtainable. The blood was counted and reported 4,250,000 red cells and 23,650 white cells.

At this time I first saw the patient. She lay in bed, the picture of exhaustion, obviously very weak, but conscious. The rash had nearly faded, although there were some traces of it still on the upper chest. The heart-sounds were clear, but weak; some râles of edema were heard in the lungs; the abdomen was flat, soft, not tender, and peristalsis was rather active. The reflexes were normal.

The condition was puzzling. There was no lack of signs, but it was difficult to interpret them. The following points were considered:

1. The profound prostration of the patient, with the weak, rapid pulse.
2. The erythematous rash.
3. The afebrile leukocytosis.
4. The intensely foul odor of the intestinal discharges.
5. The hypotension.
6. The previous history of the case.

Obviously the condition resembled some of the manifestations ascribed to toxins, although in most of these the supposed toxin is rarely, if ever, found. The profound prostration, the expression of

utter weariness, reminded me strongly of the cases of gas-bacillus poisoning that I had seen during the World War. They also had the weak and rapid pulse.

The erythematous rash was never explained. No reference to it was found in literature, none of our dermatologic friends could help us, and it is simply an observation to record.

The afebrile leukocytosis was more helpful. I have observed this in chronic or subacute pancreatitis, and I recalled dimly that I had heard it mentioned as being found in gas-bacillus infection. It also occurs in leukemia, after splenectomy, in polycythemia, and sometimes in some of the forms of pseudoleukemia. All of these could be disregarded, and the entire absence of tenderness or abdominal signs rendered pancreatitis unlikely. It reinforced the earlier thought of gas-bacillus infection.

The intensely foul odor of the intestinal discharges was merely suggestive. As nothing is known of massive infection of the intestinal tract by the gas bacillus, there is no information regarding the nature of the discharges. It seemed plausible to assume that they might be offensive, but there was no certainty. At least the cadaveric odor of muscular tissue infected by this organism was not against the assumption that the feces might be disagreeable.

The hypotension at the time was not significant, but later, after consultation with Professor Richards of the University of Pennsylvania, we realized that it might have been considered the most significant feature. During the World War, Professor Richards had been assigned the problem of studying the physiologic effects of the toxins of various microorganisms that produced gas gangrene. This work, which could it have been completed would have been extremely valuable, was interrupted by the conclusion of the war. The only definite fact that had been ascertained was the extraordinary reduction of the blood pressure of dogs to whom the toxins had been administered. Professor Richards showed us his protocols, and it is his and our hope that this work can be resumed and extended later. At any rate, it seems conclusive that these toxins cause hypotension.

The previous history at that time was misleading. Dr. Laws and I could not ignore the recent operation, although it was not demonstrable later that it had any effect upon the course of the case, excepting as it may have lowered the patient's resistance. We concluded, however, that the most reasonable diagnosis was intestinal infection with the gas bacillus. It remained to devise some method to confirm this diagnosis. A cotton swab was therefore gently introduced into the rectum, and then smeared upon a glass slide. This was repeated several times, and the slides immediately taken to the laboratory and stained by Gram's method. The picture obtained was typical, showing large, deeply-staining bacilli almost covering the slide, and was compared with several textbook

illustrations that were similar, all apparently made from smears of cultures.

An effort was immediately made to obtain some of the antitoxic serum prepared by H. K. Mulford Company against the gas bacillus. This has been used effectively in many surgical cases of gas bacillus poisoning, and it offered the only chance to prolong the patient's life. It was Sunday afternoon; the Mulford laboratory was closed, and although one of the officials promised to send us some very early Monday morning, nothing better could be done. We tried other places, but there was no serum to be had. It was then 7 P.M.

The subsequent course of the case was as follows:

7.10 P.M. Pulmonary edema commencing.

7.27 P.M. Adrenalin hydrochlorid (1 to 1000) m xx, atropin sulphate  $\frac{1}{50}$  gr., hypodermatically.

7.28 P.M. Blood pressure, 52; pulse, 116.

7.33 P.M. Blood pressure, 60; pulse, 136.

7.38 P.M. Blood pressure, 50; pulse, 140.

7.43 P.M. Blood pressure, 38. No pulmonary edema. At this time the patient was cyanosed and an attempt was made to do a venesection. This was probably inadvisable, but as the blood would not flow through the cannula, nothing was accomplished.

7.44 P.M. Adrenalin hydrochlorid, m xx was given hypodermatically.

8.12 P.M. Blood pressure, 30.

8.15 P.M. Blood pressure, 30.

8.17 P.M. Adrenalin, m xx.

8.20 P.M. Blood pressure, 30 (?).

8.25 P.M. Pulse, 140.

8.26 P.M. Blood pressure, 26.

8.34 P.M. Adrenalin, m xx.

8.35 P.M. Blood pressure (?).

8.52 P.M. Blood pressure (?); pulse, 160.

9.25 P.M. Death.

Atropin relieved the pulmonary edema. The adrenalin would have been given intravenously, but the veins were collapsed. An electrocardiogram was taken Sunday afternoon. It showed rapidity of the pulse, poor electromotive force, regular rhythm, normal conduction time, and a suggestion of muscular failure. Permission was granted for an autopsy which was performed one hour and twenty minutes after death.

**Autopsy.** Subject is an adult white female, weighing about 85 pounds, and measuring 59½ inches. Nutrition is fair, musculature fair. Postmortem rigidity is very slight but generalized. Finger nails of the right hand are purplish. Skin is dry and shows no jaundice. There are no scars, edema, abrasions or generalized adenopathy. There is a recent incision over McBurney's point, measuring 4.5 cm. It is closed with a subcuticular stitch; it is clean and is healing by primary intention. Both hands show complete syndactylism of the third and fourth fingers.

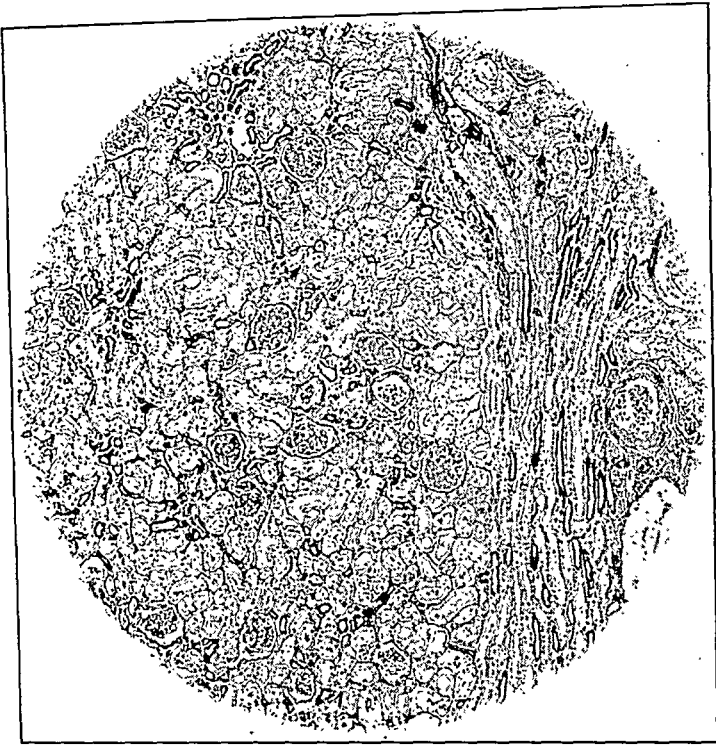


FIG. 1.—Low power of kidney, magnification 57 diameters.

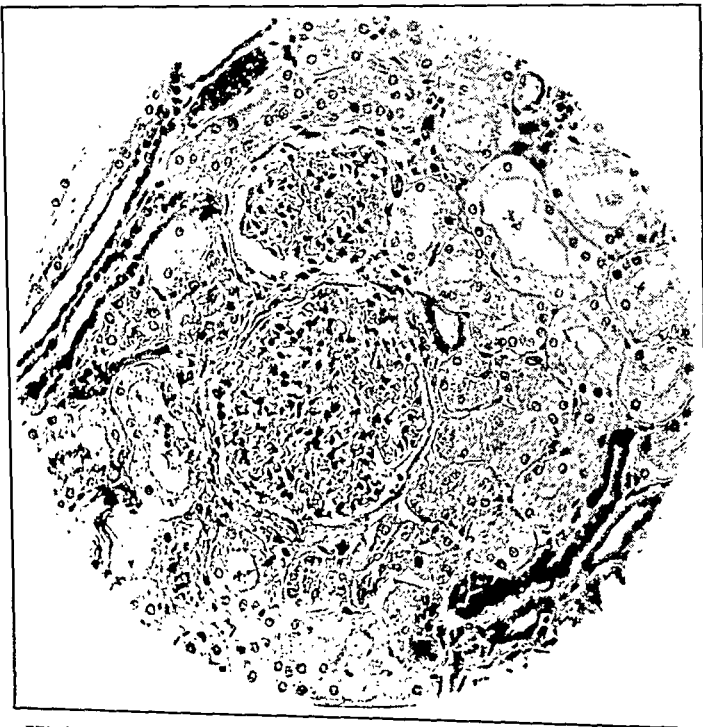


FIG. 2.—High power of kidney, magnification 230 diameters. The nuclei of cells lining capillaries of Bowman, capillaries are engorged, the spaces of Bowman contain small amounts of albuminous material and a few red cells. The nuclei of the cells lining the capsule of Bowman are swollen. The cells of convoluted tubules are swollen and granular. Lumina of tubules contain albuminous material.

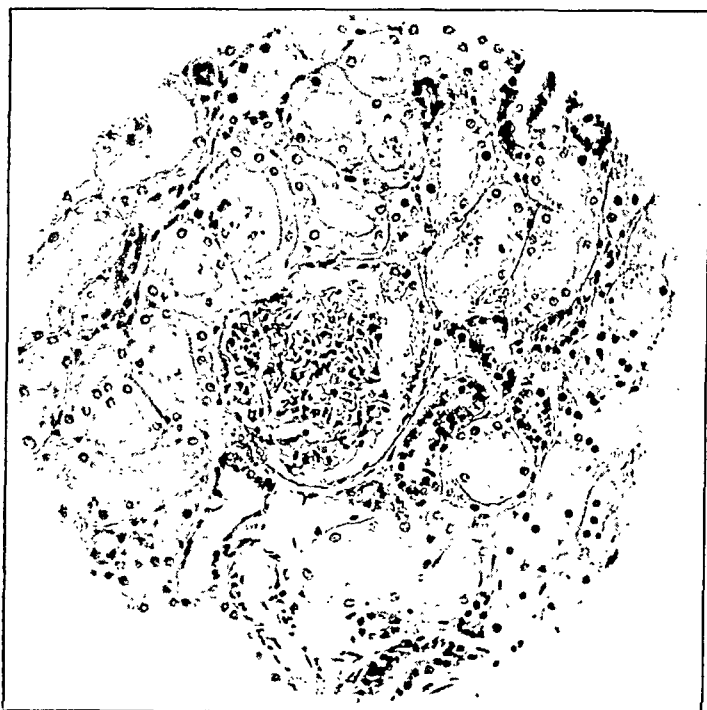


FIG. 3.—High power of kidney, magnification 230 diameters. Glomerulus shows necrosis of capillary loops.

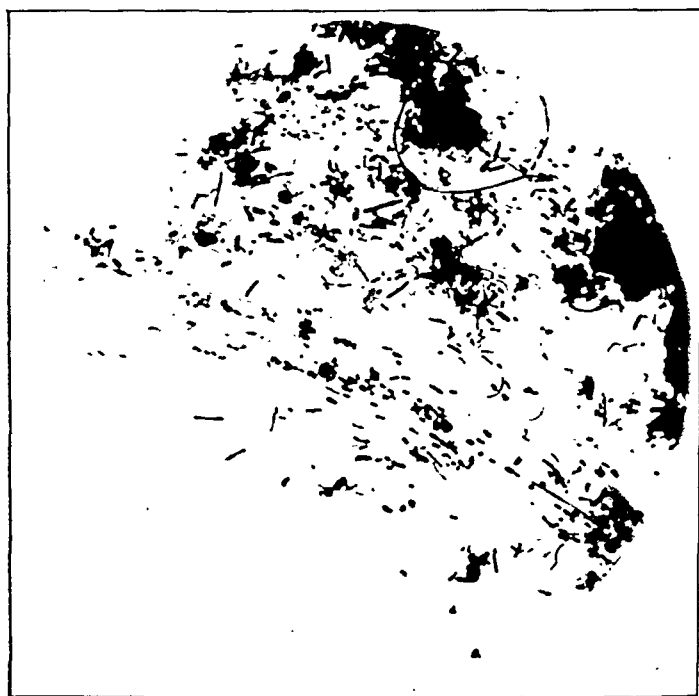


FIG. 4.—Smear from sticky mucus over ulcers in colon.

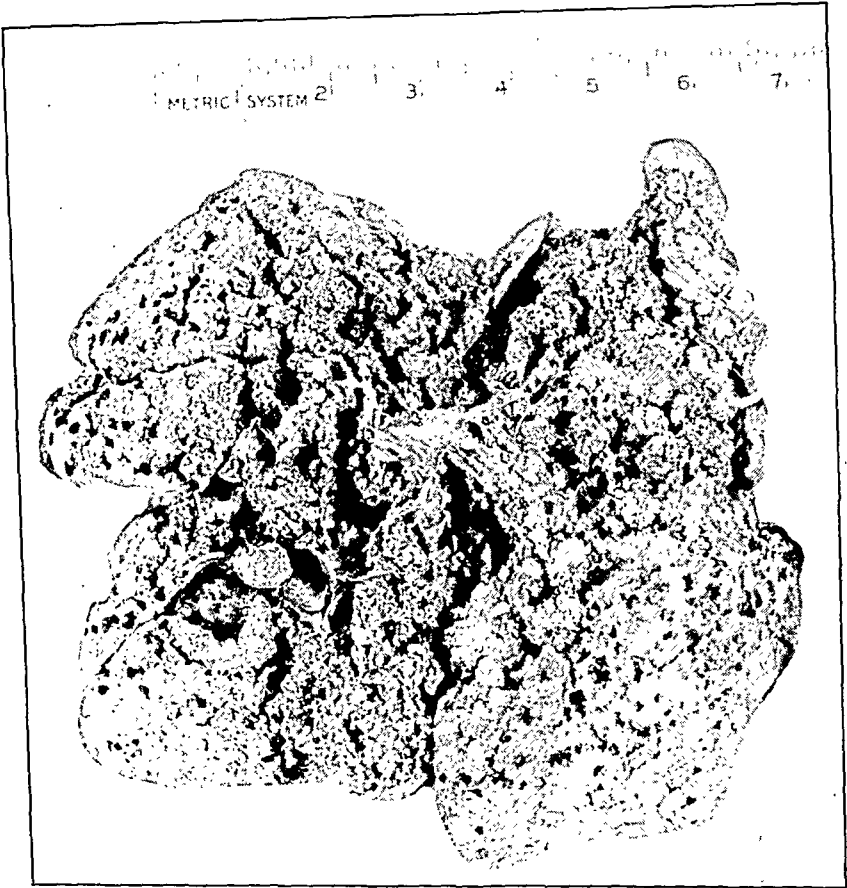


FIG. 5.—Liver of a rabbit six hours after injection of 2 cc. of twenty-four-hour culture of *Bacillus welchii* and incubation of 37° C.





*Head.* Shows no abnormalities in size or shape. *Ears and nose;* no external lesions. *Eyes:* Conjunctivæ pale, pupils smooth, round and equal, 7 mm. in diameter. *Mouth:* Mucous membranes are very pale. The teeth are in good condition.

The abdomen is flat, the wall is about 2 cm. in thickness.

*Relations of Abdominal Viscera.* Height of diaphragm: Right side, third interspace; left side, fourth interspace. Liver is 2 cm. below the costal margin in the right midclavicular line. The omentum is rather thin and is spread over the small intestines. The peritoneum is pale, smooth and glistening and contains no excessive fluid. Intestines are uniformly but slightly distended with gas; their peritoneal covering is pale, smooth and glistening. The appendix has been removed, and the stump has been inverted. The cecum at the point of inversion of the stump of the appendix is clean and does not show even small amounts of exudate or fibrin. There is no leakage. The cecum is mobile. There are several firm bands of adhesions between the lower surface of the right lobe of the liver, and the splenic flexure of the colon and the first and second portions of the duodenum. The foramen of Winslow is occluded by dense fibrous adhesions.

*Thorax.* Is long and narrow. Muscles are red in color and fairly well developed. They appear to contain more blood than usually seen. The pleural cavities are negative. The pericardium is negative.

*Heart.* Extends 1.7 cm. to the right of the midline and 6.5 cm. to the left of the midline. There are no thrombi in the pulmonary arteries. The heart weighs 170 gm. and measures 11 by 7.5 by 4.5 cm. The blood is liquid in the large vessels, but coagulated in a few minutes after being placed in a test tube. No evidence of thrombosis of the coronary vessels. Heart is contracted. The orifices and leaflets show no noteworthy lesions. Foramen ovale is occluded. Myocardium is fairly firm in consistency and brownish-red in color.

*Lungs.* Show slight passive congestion at the bases. No infarcts or other noteworthy lesions.

*Spleen.* No noteworthy lesions.

*Uterus and Adnexa.* No noteworthy lesions.

*Liver.* Weighs 1080 gm. Measures 25.5 by 22 by 7 cm. Edges sharp. Consistency, flabby. Section yellowish to brownish. Appearance cloudy; liver lobules indistinct. Amount of blood about normal.

*Gall Bladder.* Dense bands of adhesions around the neck of the gall bladder. Wall slightly but uniformly thickened. Contains thin, dark bile. Hepatic, cystic and common ducts are patulous.

*Pancreas.* Weighs 55 gm., measures 14 by 3.2 by 4.2 cm. Somewhat flabby in consistency. Lobules are distinct.

There is no evidence of thrombosis or other pathologic changes in the portal and mesenteric vessels. The mesenteric lymph nodes are moderately enlarged, the largest measuring 1 by 0.8 cm. The retroperitoneal lymph nodes are also moderately enlarged. The capsules of these nodes are rather tense and they are pale purplish-gray in color.

*Esophagus.* Negative.

*Stomach.* Negative, except for slight congestion at the cardiac end.

*Duodenum and Jejunum.* Negative.

In the upper part of the ileum are seen transversely running hemorrhagic lines; approaching the cecum they become wider so that at a point 100 cm. above the ileocecal valve hemorrhagic bands merge, and the mucosa assumes uniformly hemorrhagic appearance. The solitary lymphoid follicles are slightly enlarged but the Peyer's patches do not stand out prominently.

*Large Intestine.* The mucosa has a brownish to pearly-gray, opaque appearance. The cecum shows very numerous irregular confluent

superficial ulcers. The base of the ulcers rests on the submucous coat. In the ulcerated areas are seen slightly enlarged lymphoid follicles. The upper part of the ascending, transverse and descending colons are free from ulcers. The sigmoid shows numerous ulcers similar to those seen in the cecum. The stump of the appendix projects into the lumen of the cecum for 1 cm. The stump is occluded and there are no evidences of infection or leakage. Over the lower part of the ileum and in the colon are seen moderate amounts of thick, sticky grayish mucus, which is rather tenaciously adherent to the mucosa.

*Adrenals.* Show no gross lesions.

*Left Kidney.* Weighs 80 gm., measures 8.5 by 4.5 by 3 cm. It is fairly firm in consistency. Capsule strips easily and leaves a pale, smooth surface. Section surface does not bulge. Cortex, 7 mm. Medulla, 18 mm. Cortical striations fairly distinct. The cortex and medulla pale, pinkish to yellowish. The pyramids are purplish. The lining of the pelvis is pale, smooth and glistening.

*Right Kidney.* Weighs 75 gm. Similar to its fellow.

*Ureters and Urinary Bladder.* Negative.

*Aorta.* Negative. *Vena Cava* and branches. Negative. No gas seen in vessels anywhere.

**Microscopic Examination.** *Kidney:* The larger bloodvessels show no noteworthy changes. The cells lining the convoluted tubules are slightly granular and swollen; most of the lumina, however, remain open and contain albuminous material and partly broken-down red cells. The glomeruli appear to be rather cellular. The cellularity is due mainly to marked swelling of the nuclei, only here and there are seen dividing cells. The capillaries of the tufts are engorged, their lining endothelial cells are swollen. Only here and there is seen a necrotic loop. Only a few glomeruli show necrosis of several loops. The cells lining the capsule of Bowman are swollen in places, but there is no actual desquamation. The spaces of Bowman contain either albuminous material, red cells, or both. The collecting tubules show no noteworthy changes.

#### **Microscopic Diagnosis.**

Acute ulcerative ileo-colitis. Acute lymphadenitis of the mesenteric and retroperitoneal lymph nodes.

Early acute diffuse glomerulonephritis.

Cloudy swelling of the heart.

Toxic and fatty degeneration of the liver.

Spleen: Minor lesions.

Lungs: Slight passive congestion.

Pancreas: Minor lesions.

Adrenals: Marked hyperemia.

Blood removed from right side of the heart one and a half hours after death showed: 85 mg. per 100 cc. of blood urea nitrogen, and 640 mg. per 100 cc. of blood chlorids.

Culture from heart's blood: Negative.

Mucus from the lower part of ileum and colon shows very large numbers of Gram-positive bacilli, with blunt ends which morphologically resemble *B. welchii*. Some of this mucus was inoculated into tubes of brain bouillon. Gas was produced in a few hours. Some of the tubes were covered with a layer of paraffin oil; these tubes formed less gas. 2 cc. of a twenty-four-hour brain-bouillon culture were injected intravenously into a rabbit, and the animal was sacrificed ten minutes later. The rabbit was then placed in the incubator at 37° C. for six hours. The animal was tremendously distended with gas. There was crepitation in the interfascial spaces. The muscles were cloudy, friable, and had the appearance of having been boiled.

Characteristic odor of *Bacillus welchii* gas was noticed. The liver was studded with innumerable bubbles of gas and had a "foamy" appearance. Some of the bubbles had broken through the capsule. *Bacillus welchii* organisms were recovered on smear and culture from the heart's blood and liver. Subcultures were made in litmus milk. In twenty-four hours they showed much gas, acid reaction, coagulation, but the casein was not completely digested. At a later date spore formation was observed, which was more rapid in the paraffin-oil-covered tubes.

**Cause of Death:** Severe toxemia probably due to absorption of the *Bacillus welchii* toxin from the intestines.

**Summary.** Consideration of the clinical course and the findings of the autopsy lead us to adhere to the diagnosis of gas-bacillus infection. The changes in the kidney might, we believe, have escaped the attention of a less alert pathologist than Dr. Eiman, and moreover the lesion is too slight to be regarded as the cause of death. No other lesion was found that might be suspected, and indeed, if the *Bacillus aërogenes capsulatus* had not been found and cultured, the cause of death might have been unknown, even after the autopsy. The possibility of diabetes seems to have been definitely excluded. Apparently the most valuable signs of this condition are the profound prostration, the hypotension the afebrile leukocytosis, the peculiar fetic odor of the stools, perhaps the erythematous rash and the discovery of large Gram-positive bacilli with rounded ends in smears from the rectal contents.

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## MONGOLIAN IDIOCY: THE MANNER OF ITS INHERITANCE.

BY MADGE THURLOW MACKLIN, B.A., M.D.

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SINCE Mongolian idiocy was first differentiated as a clinical entity by Down,<sup>159</sup> its etiology has been a matter of interest, inasmuch as it frequently appeared in families in which there was no neuropathic taint.

**Theories of Etiology.** Various theories have been advanced as explanations of its occurrence, the most favorably received being those to be mentioned. Perhaps most widely accepted was the one which attributed this deformity in the offspring to reproductive exhaustion on the part of the mother, since numerous observers stated that the Mongolian idiot was usually born after a long series of pregnancies. Occasionally however, the Mongol was born in the first or second pregnancy, so that here reproductive exhaustion could scarcely be considered as the cause. In some of these instances, the mother was found to be above the average age of primiparæ or

secundiparæ, so that emphasis was placed not upon the number of pregnancies, but upon the advanced age of the mother as the causative agent. Other writers have sought the explanation for this disease in an unusual difference between the ages of the parents; in a syphilitic taint in the child; in undue emotional stress on the part of the mother during the early period of the pregnancy; in hyperthyroidism in the fetus—in immaturity or senility of the ova and in endocrine disturbances in the mother.

The very fact that such diverse theories have been advanced is fairly reliable evidence that we have not yet arrived at the correct solution. A review of the literature will convince one of the fallacies of some of these hypotheses. For example, were syphilis the underlying cause, more observers would have discovered evidence of congenital syphilis in their cases. Such evidence is remarkably lacking in the clinical reports on Mongolian idiocy, although there have been writers who have claimed to have found it in a large proportion of their patients (145). At the Mayo Clinic, where the Wassermann reaction was sought as a routine measure in such cases, not one was found to show a positive Wassermann, although the series numbered 155 patients (125). Orel<sup>131</sup> who obtained the Wassermann reaction on 65 of his 95 patients chosen at random, found it uniformly negative. Such evidence forces us to look elsewhere for the cause of Mongolian idiocy.

Comby<sup>103</sup> has been an advocate of the theory that worry or physical suffering in the early months of pregnancy is responsible. In a series of 95 cases he elicited the history of distress, either physical or mental, in 69 instances. On the other hand, many women experience suffering in the early months of pregnancy, due to the pregnancy itself, and do not produce Mongolian idiots at the end of the time. During the World War, hundreds of women were subjected to the most unusual emotional and physical strain, but only a negligible number of them brought forth Mongolian imbeciles. This theory is wholly inadequate, and must be discarded.

The idea that the disease is caused by a marked discrepancy in the ages of the parents, as for example, when the father is much older than the mother, or the mother is older than the father, might find support from isolated instances. Tumpeer<sup>152</sup> recorded a patient whose father was 66 and whose mother was 38 at the time of his birth. Cautley<sup>98</sup> reports that the mother was 38 and the father 35 at the birth of his patient. But opposed to such cases are those in which the parents are both young, and with a normal difference between their ages. They may give birth not only to one Mongol, but to two; witness, Borovsky's<sup>93</sup> cases in which the mother was 26 and 28, and the father 31 and 33 at the birth of the first and second Mongol respectively. The average of a number of cases certainly lends no support to this view. Von Hofe,<sup>116</sup> recording 41 instances found that the father was older than the mother in 36 of them.

Orel<sup>131</sup> found the mother to be older than the father in only 22 out of 104 cases. In reports in the literature, I encountered 127 instances in which the father's age was given, with an average of 39.7 years. I found 321 reports which gave the mother's age, with an average of 34.3 years. Certainly here there is no indication of undue differences existing between the ages of the parents. This theory along with the other two must be ruled out of court.

Still another fallacy to be dealt with is that concerned with the idea that advanced age of the mother is responsible for the Mongolian idiot. Let us look at the statistics for a moment. In Shuttleworth's<sup>144</sup> series of 120 cases, 66 per cent were under forty and could not have been considered as too old for a pregnancy. In Comby's<sup>103</sup> series of 93 mothers whose ages were given or indicated, 67 per cent were under 40. Orel<sup>131</sup> found that in 104 instances, the mother of the Mongol was below 40 in 67 per cent of the cases. An even higher percentage of mothers was under 40 in von Hofe's series of 36, namely, 89.

Still <sup>147</sup> states that it is rare for a woman under 30 to give birth to a Mongol, only 17 instances occurring in his 420 cases. I found 73 times that the mother was under 30 in the 321 cases listed; so that 22.7 per cent of these women were decidedly young.

The most recent literature brings out a few other hypotheses, which because they are being advocated, should receive some attention here. Clark<sup>101</sup> advances the theory that hyperthyroidism in the fetus is the cause of Mongolism. This is of interest, because cases which have been reported of hyperthyroidism in the fetus or newborn have not mentioned any accompanying Mongolism, so that it cannot be a universal factor in its production. (158, 161, 162, 163.) As a matter of fact because of the close similarity between cretinism and Mongolian idiocy, the latter has been attributed to a deficiency in the thyroid during fetal life (112, 120), although thyroid administration has repeatedly failed to relieve this condition.

Mackintosh<sup>123</sup> attributes the disease to fertilization of ova that are immature or too senile to develop into a perfect fetus. He states that the Mongol is usually found as the first child of a very young mother, or one born when the mother is nearing the menopause. For cases that occur in between these ages, he postulates a pathological degeneration of the ovary occurring any time during the sexual life of the mother. In the combined 197 cases cited by Orel<sup>131</sup> and Comby<sup>103</sup> the mother was below 20 only twice, so that sexual immaturity played no part in these cases. With respect to the advanced age of the mother, we found 67 per cent under 40 with the average 34.3 years, an age removed from the time of the menopause by 10 or more years.

For all the cases not covered by the immature or senile aspects of his theory, Mackintosh brings forward the pathological degeneration of the ovary as an explanation. Since both ovaries may not

degenerate at once, he says that a woman may give birth to two, but only two Mongolian imbeciles in her life. The corollary of this proposition is that after the birth of the second Mongol, no child, normal or affected could be born. There are, however, records in which four Mongols in a family were born (90); and three in which three were present (48, 114, 140). In one instance (140) the three Mongols were preceded and followed by one normal child. In a second case, the defective offspring were the first, fourth and sixth of six children (114). In another family in which there were two Mongols, they were the first two children, and were followed by three normal ones. Mackintosh's theory of the etiology of Mongolism falls to the ground, condemned by recorded facts.

Armstrong<sup>89</sup> feels that the cause is maternal, operating at maturation. He does not state that he believes it to be hereditary in origin. Greig<sup>112</sup> considers that the disease has its origin in a defect in fetal growth. He conceives it to be an inability on the part of the fetus to continue development along the lines laid down in the early or embryonic period. While it is true that the effects of this disease may not be manifest until the fetal period, the primary cause was present I believe in the unfertilized ovum and in the sperm as well.

That the sperm is as much responsible as the ovum is supported by the pedigree reported by Hermann<sup>114</sup> in which the grandfather of one Mongol, and the grandmother of another were brother and sister. This is suggestive at least that the defective germ plasm was present in this brother and sister, and was passed on down to their grandchildren.

Now let us turn to what is perhaps the most favored of the theories, namely, that the Mongolian idiot is born at the end of a large family, and that the condition is due to reproductive exhaustion. After a rather thorough search through the literature, I was able to collect records of 275 cases of Mongolian idiocy in which the place in the family occupied by the defective child was stated. From these figures a curve was constructed showing the percentage of the total number of cases which occurred in each place in the family (Fig. 1 broken line). It will be noted that 28 per cent of all the cases were the first child in the family. Only 15 per cent of Still's<sup>147</sup> 420 cases, and 22 per cent of Orel's 95 cases were the first born of their families. This is an average of 20 per cent for the 788 cases listed in Still's, Orel's and my series.

Reference to this curve shows that 69 per cent of the number (190 cases) of affected patients were the result of the first four pregnancies, so that most of them could not have been attributed to reproductive exhaustion. In 300 cases reported by Reuben and Klein<sup>137</sup> (not included in my list), there were 50 per cent who were the result of the first three pregnancies. Although Still<sup>147</sup> is inclined to look upon the number of pregnancies as playing some rôle in the

production of this condition, his figures show that over half the cases, 54 per cent, fell into the place of the first four children of the family.

When we compute a curve for the entire families from which these patients came, we see that of the 1100 members making up these families, 738 or 67 per cent were the first four children of the family (Fig. 1, solid line). What does this very close approximation of figures mean: 69 per cent of the defectives and 67 per cent of the entire families occurring in the first four pregnancies? As I interpret them they mean this—the Mongolian idiot tends to occur in each place in the family in the same proportion that the population

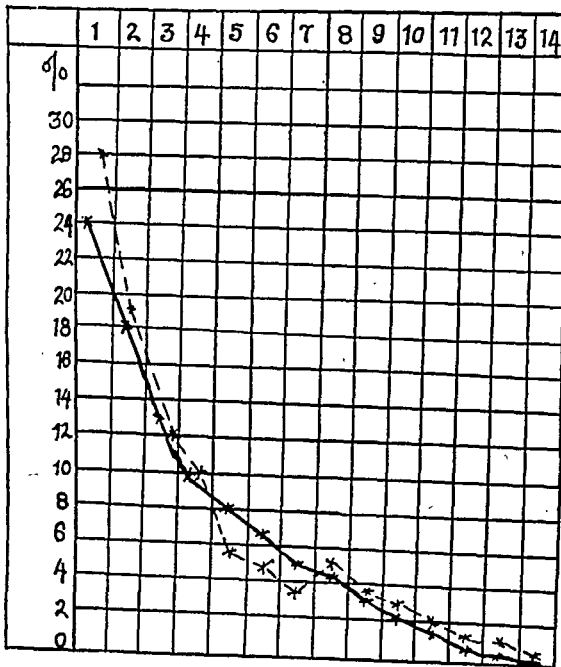


FIG. 1.—Based upon 275 cases of Mongolian idiocy, showing the percentages of the total number of cases which occur in each place in family, in broken line; while the solid line, based upon 1100 members which constituted the families from which the Mongols came, shows the percentages which occur in each place in family. Sixty-nine per cent of the affected and 67 per cent of the entire number occurred in the first four pregnancies.

as a whole occurs in these places, showing that there is no greater liability for the Mongol to be born at the end of a large family, than there is for it to appear at the beginning or middle of it.

We may attack this problem from a slightly different angle, namely, by determining the average pregnancy at which the defective offspring appeared. Brushfield<sup>96</sup> in his series of 157 cases (not included in my statistics) found that the average pregnancy which resulted in the birth of a Mongolian idiot was the fourth, the average from the 275 cases in the literature was 3.8. Although Still does not compute this figure it may easily be derived from his curve, the result being 4.9. There is thus remarkable uniformity in the values from three different series of cases.



Here might be mentioned the tendency to report the Mongol as the "last" child, implying that it comes at the end of the reproductive period of the mother. It might be the last child and yet be the result of the first pregnancy. Moreover, if there has been no time for a second pregnancy to supervene after the birth of the defective child, it is inevitably the "last" at that time. Hence statistics saying that it was the last child in 50 or 60 per cent of the cases do not prove anything at all. Von Hofe<sup>116</sup> points out this error and illustrates his point from his own series. Of 150 cases the Mongol was the last child in 97 cases, but in 70 of these 97, the child was under two years of age. There had scarcely been time for another pregnancy to occur. Were these families to be investigated ten

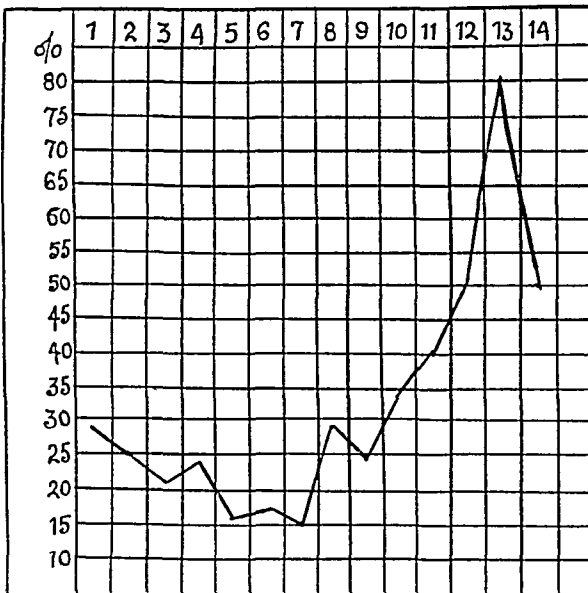


FIG. 2.—Showing the ratio of affected to normal individuals in each place in the family. The curve shows an upward trend at the end, but compare this with Fig. 6, based upon similar ratios in the case of families with 1600 members suffering from hereditary defects. These far from being looked upon as more apt to affect the later children have been held to be prone to affect the *first* child. The upward trend of both is explained by the few cases upon which the ratios in these places are founded.

years from now, the Mongol would stand less chance of being the last child. Berry<sup>91</sup> reports 10 instances in which a normal child followed the birth of the defective one. Brushfield<sup>96</sup> in 157 cases, found that six times the Mongol was followed by one normal infant; five times it was succeeded by two normal children; twice it was followed by three; once each by four, five and seven! If reproductive exhaustion be at the basis of this defect, what must have been the mother's condition after bearing seven more children following the Mongol! Comby<sup>103</sup> records 6 cases; Fletcher<sup>110</sup> one and von Hofe<sup>116</sup> one, in which the Mongolian idiot was followed by one or more normal children. Although these are by no means the only

instances in which the defective child was not the "last," they will suffice to show that this idea is without foundation in fact.

Ordahl<sup>129</sup> finds that twelfth children are affected four times as frequently as they are expected. In the series I have collected, those who are affected and fall in to the twelfth place in the family are twice as numerous as they should be according to the percentage in twelfth place in the entire family, but exactly the same thing holds true for the twelfth children in amaurotic idiocy. Thus 0.7 per cent of all the children in the Mongolian families were twelfth, but 1.4 per cent of the *affected* children were twelfth. But in amaurotic idiocy, the corresponding percentages are 0.3 for the population as a whole, and 0.6 for the affected children. The number of cases which one finds among twelfth children are so limited in number, because there are so few families which are that large, that statistics become unreliable. Thus in Fig. 2, which represents the ratio of affected to unaffected in the Mongol families, we see the curve rise sharply at the end, which might be interpreted to mean that the later pregnancies produce an unduly large proportion of the Mongols. But if we compare this with Fig. 4, which is similarly plotted for the ratios of affected to normal in amaurotic idiocy, we see this curve rises toward the end. Fig. 5 (reproduced from another paper which has not yet appeared in print) is a similar curve for 1600 cases of hereditary defects, and here again the curve which has varied on either side of a theoretical line representing the average for these percentages, rises abruptly for the thirteenth, fourteenth and fifteenth child. Yet such defects have been held as most liable to affect the *first* child of the family.<sup>139</sup> Thus we see that it is due to the limited number of cases found in these later pregnancies that the curve fluctuates so widely. The type of defect whose incidence is being shown in the curve, whether it be Mongolism, amaurotic idiocy or hereditary defects in general, does not appear materially to alter the shape of the curve (Fig. 2).

**Summarized Objections to Theories of Etiology.** To sum up briefly then the inconclusiveness of the theories thus far dealt with: syphilis, far from being universally found in these cases, is comparatively rare. There are too many instances in which the mother has endured physical or mental hardship during the pregnancy and does not produce a Mongol, for us to designate this as a cause. Most cases occur when the age differences between the parents is that usually found in the population at large. The average age of mothers producing Mongolian idiots was 34.3 years, and of the total number of cases, 22 per cent were less than 30. The average pregnancy which resulted in the defective child was about the fourth, and 69 per cent of the total number of defectives were found to occur in the first four pregnancies.

**Mongolian Idiocy in Twins.** But the fact which forces us to abandon all these arguments is not the statistics which show how old or

how young the mother was; or that it was the first or the fifteenth child who was the Mongol, but the fact that with the passing years, there are accumulating more and more instances in which at the time the Mongol is born, there is born also a normal twin.

It is at once obvious that if difference in age of the parents, or advanced age of the mother, or uterine exhaustion or endocrine disturbances (141) or any other environmental influence is to have any effect upon the developing fetus in the direction of producing a Mongolian idiot, then both twins should be affected. That they are not is a matter of record. Thus Mitchell and Downing<sup>127</sup> found that in 24 instances in which Mongolism had been reported in twins before 1926, there were only 3 cases in which both twins were affected. They were of the same sex. In the remaining 21 cases only one-half the contents of the uterus was affected, the other half being a normal twin:

Thus in the majority of instances the evidence is strongly against environmental influences, and much in favor of the defect being inherent in the germ cell, that is, inherited. This conception would at once explain the occurrence of twins one of which was normal, the other defective. But there comes in at this point the consideration of uniovular and biovular twins. If from two ova it is not necessary that they be alike, either in sex or characteristics; although they may be, but if they are derived from one ovum then they must be identical with respect to both these features. But we must remember that although the twins are of the same sex they are not necessarily from the same ovum. An article just published by H. H. Newman<sup>160</sup> discusses the method of diagnosing identical twins, and there are instances, even after the most exacting scrutiny, in which it is almost impossible to decide whether they are merely fraternal, or are identical. This must be remembered when we come to examine the reports of the cases in the literature. Since the report of Mitchell and Downing, I have collected 10 other cases in which this disease occurred in twins, and these with Mitchell's cases and 14 others reported by Orel<sup>130</sup> are tabulated in Table I.

There are listed here 48 cases of Mongolism in twins, involving one or both members. One of these (see Table I) is doubtful, the diagnosis between congenital syphilis and Mongolian idiocy not being clear. Of the 47 authentic cases, there are 17 in which the twins were of opposite sex, obviously biovular, and in which only one was affected. There were 6 cases in which both twins were affected and both were of the same sex, presumably uniovular. In 4 cases the sex was not given of either twin, but only one was affected. There were 20 cases (not including van der Bogert's) in which the twins were of the same sex, but only one was affected. In 5 of these the record says definitely that there were 2 placentæ or that they were biovular (108, 113, 127, and Moro and Siebert,

TABLE I.—MONGOLIAN IDIOCY IN TWINS.

Author.	Male.	Female.
<i>Cases in which sex differed.</i>		
Neumann, 1899 (cited by Orel, 1926)	■	○
Shuttleworth, 1909	□	●
Hultgren, 1915 (cited by Orel, 1926)	■	○
Cassel, 1917 (cited by Orel, 1926)	■	○
Cassel, 1917 (cited by Orel, 1926)	□	●
Swanberg and Haynes, 1919	■	○
McLean, 1922	■	○
Halbertsma, 1923	■	○
Halbertsma, 1923	■	○
Halbertsma, 1923 (cited by Orel, 1926)	■	○
Peiper, 1923 (cited by Orel, 1926)	□	○
Vas, 1925 (cited by Orel, 1926)	□	●
Orel, 1926	■	○
Comby, 1927	■	○
Comby, 1927	□	●
Krabbe, 1927 (cited by Orel, 1927)	□	●
Armstrong, 1928	■	○
<i>Cases in which the sex was identical with one twin affected.</i>		
Halbertsma, 1923	□ ■	
Halbertsma, 1923		○ ●
Siebert, 1923 (cited by Orel, 1926)		○ ●
Moro, 1923 (cited by Orel, 1926)		○ ●
Clay, 1922		○ ●
Jewesbury, 1925	□ ■	
Myers, 1925		○ ●
Cassel, 1926* (cited by Orel, 1926)	□ ■	
Orel, 1926		○ ●
Gautier and Coetaux, 1926 (cited by Orel, 1927)		○ ●
Coupland (cited by Greig, 1927)		○ ●
Coupland (cited by Greig, 1927)		○ ●
Dietrich and Berkley, 1926		○ ●
Deitrich and Berkley, 1926	□ ■	
Wieland, 1926 (cited by Orel, 1927)		○ ●
Mitchell and Downing, 1926		○ ●
Chown, 1927	□ ■	
Krabbe, 1927 (cited by Orel, 1927)	□ ■	
Krabbe, 1927 (cited by Orel, 1927)	□ ■	
Krabbe, 1927 (cited by Orel, 1927)		○ ●
Van der Bogert, 1916†	□ ■	○ ●
<i>Cases in which twins were of same sex and both affected.</i>		
Hjorth, 1906* (cited by Swanberg and Haynes)		
de Bruin, 1902 (cited by Halbertsma)		
Strauch, 1923	■ ■	
Brückner, 1926	■ ■	
Reuben and Klein, 1926		● ●
Dickey, 1927	■ ■	
<i>Cases in which sex of twins was unknown, one affected.</i>		
Fraser and Mitchell, 1877 (cited by Orel, 1926).		
Halbertsma, 1923.		
McKee, 1919 (cited by Swanberg and Haynes).		

Weigall (cited by Halbertsma).  
 \* Sex not given.

† This case, in which one of male twins was affected, as well as an older sister of the twins, is doubtful, although Orel, 1926 includes them in his list as authentic cases. They were first shown as undoubted cases of Mongolian idiocy, but later as cases of congenital syphilis simulating Mongolism. The Wassermann test in the sister and affected twin was positive and negative in the normal twin brother.

cited by Orel<sup>131</sup>). In 14 of the remaining 15 cases, there is no evidence presented one way or another.

In Wieland's case, it is stated that they were diagnosed in the obstetrical clinic as *uniovular*. If this were true, it would be such strong evidence against the theory that this defect is hereditary that it would practically mean its abandonment. But Orel,<sup>131</sup> who cited this case, does not state whether Wieland gives the evidence upon which this diagnosis was made, and inasmuch as it is the only case in 47 that appears to controvert the evidence, I feel that we may take with considerably more than the traditional allowance of salt the statement that in this case the twins were from a single ovum.

**Importance of the "Short Little Finger."** Before going into a discussion of the mode of its inheritance, there is another matter that should be mentioned in this connection. In a great many of the clinical reports of Mongolian imbecility, mention is made of the presence of the short little finger, which does not reach up to the terminal joint on the ring finger; also of the incurved distal phalanx of the little finger; and in some instances the transverse line across the palm which divides it completely into two regions. Thursfield<sup>151</sup> in a study of his cases found that the incurved phalanx was absent in 16 cases, present in 13 and not noted in 13. Thus in the observed cases it was more often absent than present. Orel<sup>131</sup> found it present in 39 of 69 observed cases. Crookshank,<sup>105</sup> states that it has no special relation to Mongolism but occurs in the young of all races, and that not infrequently it is hereditary. I wish to mention here a family in which the short little finger with marked incurving of the last phalanx has been transmitted through the direct line for four generations, having been present in a woman, her daughter, two of her daughters, and a daughter of one of these. In addition to this, in the female of the fourth generation and in her mother there was present also the transverse line across the palm. Evidence as to the presence or absence of this feature in the other three was not noted. The intelligence in all these women was decidedly above the average. Wile<sup>157</sup> found this transverse line in 8 of 25 cases of Mongolism.

Wegelin<sup>155</sup> reported a family in which this defect, namely, a short little finger with the distal phalanx showing incurving, was transmitted with great frequency and as a dominant character. Orel<sup>130</sup> found that this condition had existed in four generations in the family which finally produced the Mongolian idiot which was one of his patients. The condition had been present in a woman, her son, six of his eleven children, and in two of the children of one of these who was affected, so that it behaved as a dominant character. Orel<sup>130</sup> cites the opinion of one writer that this condition in the hand may be indicative of a latent tendency toward Mongolism, which together with exogenous factors will produce outspoken Mongolian

idiocy. Although in Orel's case the mother who produced the Mongol had herself the deformed little finger, there was no exogenous circumstance that could account for the production of the defective child, especially since that pregnancy terminated in a normal child as well, and since the mother four years later produced another normal child.

Of course there are all grades of this defect, and a mere glance at the hands of many of the population serves to show how frequently the milder grades are seen. Certain it is that it is found in many individuals who are far from showing Mongolism, and that Mongolian idiots are frequently found in whom this particular characteristic is lacking.

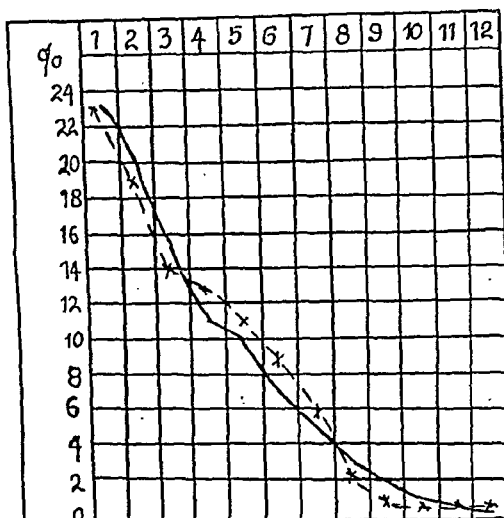


FIG. 3.—The solid line shows the percentages of the total membership of 118 families in which amaurotic idiocy occurred which fell into each place in family. The broken line represents similar percentages for the affected members of these families. Note the practical identity of the two curves, also that 69 per cent in both cases were the result of the first four pregnancies.

**Method of Inheritance of Mongolian Idiocy.** As noted in the foregoing paragraphs, there is good evidence in support of the theory that this condition is an hereditary one, and very conflicting evidence in support of any of the theories which attribute it to factors other than those residing in the germ cell. If it is inherited, what is the mode of its transmission; is it due to unit recessive factors as suggested by Hermann?<sup>114,115</sup>

If the reader will recall the matings of individuals showing dominant or recessive characters as worked out by Mendel over sixty years ago, he will remember that if a trait, normal or defective, be dominant, it must be present in at least one of the parents in order that it appear in the children. In the disease under discussion, there are, so far as I am aware, only two records of a Mongolian idiot having had a child (134, 139), and in these cases all three children were normal. In every instance in which a child was a Mongolian

idiot the parents were normal, at least as far as idiocy of the Mongolian type was concerned. That at once rules out the possibility of its being a dominant character. If the trait is recessive, there is one mating in which both parents being normal may yet produce a defective child, namely, that mating where both parents are hybrids,  $DR$ , and in which the offspring are apt to appear in the ratio of three normal children ( $DD$ ,  $2 DR$ ) to one abnormal ( $RR$ ). Such a unit recessive character Hermann<sup>114,115</sup> thinks Mongolism to be.

Let us examine the question with the aid of the statistics gathered from the literature, and compare these with the figures of other diseases due also to recessive factors, presumably unit. For comparison let us choose amaurotic family idiocy, which always appears in offspring of normal parents, and hence must be due to recessive characters. In the literature available to me, I was able to collect records of 118 families in which amaurotic family idiocy occurred,

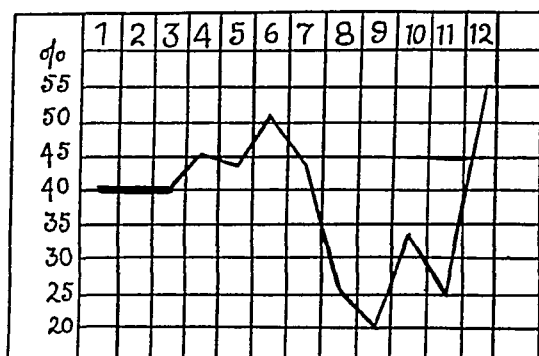


FIG. 4.—The ratio of affected to normal members in these 118 families. The curve rises at the end in a manner similar to that in Fig. 3 and Fig. 5.

and in which the order of the children was given. In addition to this there were 24 families recorded in which the order of children was not given. In Fig. 3 are plotted two curves, the broken line being the percentages showing the distribution of these affected individuals in the family. The curve for the place in family of all the members, affected and normal, is given in the solid line for comparison.

Thus in 118 families there was a total of 509 persons distributed through twelve places. Of these, 118, or 23 per cent, were the first born of their family; 100, or 20 per cent, were the second born, etc. The broken line represents a similar set of percentages for the affected persons in these 118 families. There was a total of 210 affected persons, of whom 48, or 23 per cent, were the first born; 40, or 19 per cent, were second born. A glance at Fig. 3 shows how closely these two curves approximate each other, indicating that there was no greater tendency for this disease to appear in the children from the earlier pregnancies than in those from the later ones,

or *vice versa*. Of these 509 persons, 354, or 69 per cent of the members, occurred in the first four pregnancies. Of the 210 defective children, 145, or 69 per cent, likewise occurred in the first four pregnancies. This shows again, as do the two curves, that in a family in which this disease is apt to occur, any one child is just as liable to show it as any other.

It was mentioned above that, in addition to the 118 families in which place in family was given, there were 24 other families found in which the disease occurred. Of these 142 families there were 68 in which only one child in the family was affected, and 74 families in which more than one was affected, distributed as follows: 29 had 2 defective children, 29 had 3; 11 had 4; 3 had 5; 1 had 6 and 1 had 8 amaurotic family idiots to its credit! Thus, of the total number of families listed, 74, or one family in every 1.9 families, had more than one member affected. These 142 families had a total of 279 affected children, or an average of 1.96 to a family.

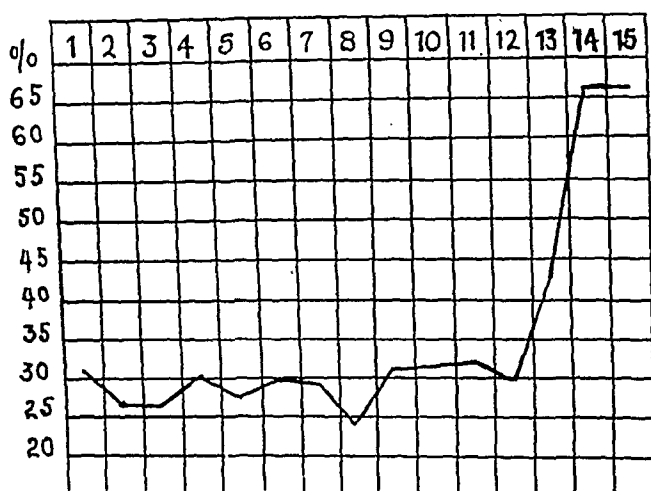


FIG. 5.—The ratio of affected to normal individuals in families in which occurred 1600 persons with hereditary defects. The same rise at end of curve as seen in Fig. 3, due to limited number of cases found in these later pregnancies.

Let us now compare these figures with those obtained in an exactly similar manner for Mongolian idiots, a disease far more frequent than amaurotic idiocy, for where I found only 142 families affected with the latter condition, I found records of 2491 families in which Mongols had been born. Of these the place in the family was indicated in 268 instances; the number of affected being 275. Fig. 1 gives the curve for the place in family of all the members in a solid line, and a similar curve for only the affected persons in these families in the broken line. Again there will be noted a rather close agreement between the two, thus indicating that there is not any undue tendency for the Mongol to appear in the later pregnancies. As a matter of comparison, 190 of the affected children, or 69 per cent occurred in the first four pregnancies, while 738, or 67 per cent



of the children of these families were the first four of the family. It will be noted that just the same percentage of Mongols as of amaurotic idiots appeared in the first four pregnancies, namely, 69. Still's standard curve shows that only 63 per cent of the whole population occurs in the first four pregnancies. There never has been held to be any special predilection on the part of the late pregnancies to terminate in an amaurotic idiot; there should be no theory that the Mongolian idiot is more apt to occur at the end of a large family in the face of figures like these.

Of these 2491 families, in which occurred 2526 Mongolian idiots, there were 2461 in which only one child was affected, and but 30 in which more than one was a Mongol. There was one instance in which four were affected (90); three in which three Mongols appeared (48, 114, 140); and 26 families in which there were two Mongols (93, 104; 108; 111 same as 132; 114, 2 cases; 123; 132; 137; 140; 142; 145; 154, 130, 9 cases; 131, five cases). In addition to these cases in which brothers and sisters were affected, there were three instances in which first cousins were affected (93, 99, 133), one in which second cousins were Mongolian idiots, (114) and one instance in which a woman who had two sisters and one brother affected, gave birth to a child similarly afflicted (114). Thus, although there was one family in every 1.9 which showed familial distribution in amaurotic family idiocy, there was only one in every 83 families which showed more than one child affected with Mongolian idiocy. While the average number of affected per family in the former disease was 1.96, it was only 1.014 for the latter.

Even the most casual glance at these figures will convince the average reader, that if both these diseases are due to recessive factors, amaurotic family idiocy is due to factors which make the appropriate combination far more frequently than do those responsible for Mongolian idiocy; almost 44 times as often according to the above figure. What then is the explanation of the wide difference in the two diseases, one occurring frequently in families, the other rarely, since both are stated to be hereditary, and due to recessive factors?

Let us assume for the moment (a statement that has indeed been assumed for a long time) that amaurotic family idiocy is due to a combination of two recessive factors,  $RR$ . Since it always occurs in the children of healthy parents (for the affected child always dies in infancy and never lives long enough to become a parent) the parent's genetic constitution must be  $DR$ , so that the chances are 1 in 4 that the defective child will be born; 3 in 4 that the children will be normal. Do the figures of amaurotic family idiocy agree with these theoretical ones? We found that of 509 persons, 210 were affected, or 41 per cent. We should have expected only 25 per cent. Where is the difficulty?

From statistics gathered in connection with hereditary conditions

in which the number of families having 1, 2, 3, and so forth, children was determined, I found that in a total of 200 families, there were 41 with only one child, 33 with two; 28 with three; 22 with four; 18 with five; 15 with six; 12 with seven; 9 with eight; 8 with nine; 5 with ten; 4 with eleven; 2 with twelve; and one each with thirteen, fourteen and fifteen children respectively.

**Experimental Studies.** I then set myself the task of determining how many children with amaurotic family idiocy would be born in 200 families, in which the genetic constitution of the parents was *DR* and in which one would expect that one in every four would be defective. The method chosen was simple and not without errors. It is not even thought that such a procedure as that to be described proved the method of inheritance in amaurotic family idiocy or in Mongolian idiocy. The results obtained were interesting, however, when compared with the figures obtained from the literature of actual cases.

For the so-called theoretical cases of amaurotic family idiocy, I chose three red balls, and one white; placed them in a box, in the bottom of which was a hole slightly larger than the diameter of the balls, which were of the same size and weight. These were then shaken up, the box turned upright and a ball allowed to roll out. If red, it was regarded as a normal child, if white it was listed as defective. This was done 847 times (that being the total number of individuals in the 200 families mentioned above). These were divided off into families of appropriate size, and the position of the defective child in its respective family noted. Thus, of the 200 families in which the white ball might have appeared, it did so in only 122, but appeared in these 122 families 205 times. There were 68 in which the white ball appeared only once, and 54 in which it appeared more than once. Thus there was one in every 2.2 families affected, a number not far off the 1.9 actually found from the literature. These 122 families had 205 affected, an average of almost 1.7 to a family—a number, again, not far from the actual 1.96 per family. There were 143, or 69 per cent of these 205 cases that occurred in the first four pregnancies, exactly corresponding with the percentage actually found for that value.

Now it will be recalled that there were 847 opportunities for the white ball to appear; it actually came out 205 times, or once in every 4.1 times as against the theoretical 1 in 4. The law of chance was working rather smoothly here. On the other hand, the 205 times were grouped in 122 families, with a total membership of 661. This means that instead of 25 per cent of these families there was here 31 per cent, affected. Compare this with the high value of 41 per cent found in the real families. This explanation is probably the one at the basis of the too high percentages in actual cases. We do not know the number of families who have the potentiality of producing an amaurotic idiot who do not do so. If we did, and added

the number of pregnancies in them which result in normal children to our calculations, we should inevitably find a decrease in the value of 41 per cent. What this decrease would be is, of course, impossible to say. The close agreement between these theoretical families and those found in the literature is interesting to those who believe that this condition is inherited and is due to a combination of unit recessive factors.

It will be recalled that Mongolian idiocy though much more frequently encountered than amaurotic family idiocy, is, however, very rarely familial in distribution as compared with the numerous instances in which amaurotic idiocy affects more than one member of the family. Were it due to a unit recessive factor, its chances of affecting more than one child in a family would be identical with amaurotic idiocy, and so we should expect to find that instead of 30 families with more than one Mongol, there would be 1311 families showing familial distribution. Obviously, Mongolian idiocy is *not* due to a pair of *unit* recessive factors.

If we suppose that it may be due to a combination of two pairs of recessive factors then the chances for its appearing in more than one member of a family would be lessened, the degree to which that lessening took place depending upon the genetic constitution of the parents. For example, let us suppose that there are two factors, *A* and *B*, dominance of which is expressed by capitals, recessiveness expressed by small letters, and that it is only when the genetic constitution of the individual is *aabb* that Mongolism results. Then the parents could be a combination of any of the following constitutions; (1) *AaBb*; (2) *aaBb*; (3) *Aabb*, each one of which would be normal, in itself, but capable of producing a Mongol if the proper combination were made. The percentages of defective offspring would vary according to the combination of parents.

In Table II one sees that of the six possible combinations, there are three which give chances of 1 in 4 for the appearance of the defective offspring, *aabb*, two in which the chances are 1 in 8, and one in which they are 1 in 16. If these three parental types were present in equal numbers in the community, and if the 6 possible combinations of these types were made in equal numbers, the chances for the Mongol to appear in these families as a whole would be 1 in 7.

Taking the combination which produced Mongolian idiots in the ratio of one idiot to 15 normal individuals, as the basis for the theoretical families, the balls were now placed in the box, 15 red and one white one, and the series of 200 families completed as has been described. Here out of a possible 200 families in which the defective child might have occurred, it actually appeared in but 50. In these 50 families there were 6 in which the white ball appeared more than once. Thus, one family in every eight showed familial distribution. There was a total of 59 affected, or an average of 1.18 to a family. That there was adequate mixing of the balls, so that

the law of chance had full sway, is shown by the fact that of the total number of balls thrown out (847) only 59 times did the white ball appear. One-sixteenth of 847 is 53, so that the number 59 is not far off the theoretical value.

It will be noted, however, that these theoretical figures indicate that there should be several members of a family affected far more frequently than there are actually. Hence we may conclude that the inheritance of Mongolian idiocy is a much more complicated matter than dependence upon unit recessive factors or upon two pairs of recessive factors. As was noted above, it is sometimes associated with the presence of peculiarities in the hand that are definitely inherited in some families, apparently as simple dominant characters. Whether associated with several recessive characters,

TABLE II.—COMBINATIONS OF TWO PAIRS OF RECESSIVE CHARACTERS.

COMBINATION 1 BY 1.					
	egg	AB	Ab	aB	ab
sperm AB		AABB	AABb	AaBB	AaBb
Ab		AABb	Aabb	AaBb	Aabb
aB		AaBB	AaBb	aaBB	aaBb
ab		AaBb	Aabb	aaBb	aabb
COMBINATION 1 BY 2.					
	egg	AB	Ab	aB	ab
sperm aB		AaBB	AaBb	aaBB	aaBb
ab		AaBb	Aabb	aaBb	aabb
COMBINATION 1 BY 3.					
	egg	AB	Ab	aB	ab
sperm Ab		AABb	AAbb	AaBb	Aabb
ab		AaBb	Aabb	aaBb	aabb
COMBINATION 2 BY 2.					
	egg	aB	ab		
sperm aB		aaBB	aaBb		
ab		aaBb	aabb		
COMBINATION 2 BY 3.					
	egg	Ab	ab		
sperm aB		AaBb	aaBb		
ab		Aabb	aabb		
COMBINATION 3 BY 3.					
	egg	Ab	ab		
sperm Ab		AAbb	Aabb		
ab		Aabb	aabb		

there are one or more dominant characters, will remain a mystery, inasmuch as we cannot make the appropriate mating experiments for the solution. It is interesting to speculate, however, concerning the mode of inheritance, and inasmuch as there are numerous instances of Mongolian idiocy in which these hand peculiarities are lacking, it may be that it is dependent upon recessive factors alone, unassociated with the presence of any dominant factors.

For the sake of carrying the analysis a step further, let us assume that the condition of Mongolism is dependent upon the simultaneous presence in the mature germ cell of *three* pairs of recessive factors carried in three different chromosomes. Then the chances for the meeting of the factors to produce the proper combination, *aabbcc*, are only 1 in 64 if the parents are both hybrids with respect to all three factors. As in the case of the two pairs of factors, there are other combinations possible, but inasmuch as they all give more frequent opportunity for the combination representing the defective one, they will be disregarded for the moment.

When choosing the balls which should represent the combination

in which the chance for the defective offspring to appear was 1 in 64, the 63 colored balls were chosen of seven different shades, so that I might judge by the color which came out each time if there were adequate mixing of the balls in the box, a fact I could not have decided had they all been of the same color with the exception of the white one. With increase of the difficulties attendant upon the appearance of the white ball, the number of times which it appeared in the set of 200 families became so small as to make results unreliable; so that instead of 200 families with a total of 847 members, the occurrence of this defect was sought in 600 families with a total of 2541 members. In the first 200, the white ball came out 13 times, in the second 200, 14 times, and in the third 200, 13 times, but twice it occurred in the same family. Thus it occurred 40 times in 39 families, or an average of 1.02 to a family, a value in close agreement with that actually found, namely, 1.014.

That there was adequate mixing of the balls is shown by the fact that one-sixty-fourth of 2541 is 39.7, while the actual number obtained was 40. One family in 39 showed familial distribution as compared with 1 in 83, actually found from the literature. This "familial" instance, however, did not occur until I had come to the thirty-eighth family with an affected member. Hence it might well have been that had I made another attempt to find how often it occurred in a second 600 families, I might have gone well up toward the 80 mark before encountering a second "familial" case.

**Further Discussion.** But, as was mentioned, the combination of parents in which the chances for a defective offspring are 1 in 64 is by no means the only possible one. There are seven possible types of parents, *AaBbCc*, *AaBbcc*, *AabbCc*, *Aabbcc*, *aaBbCc*, *aaBbcc*, *aabbCc*, with 28 possible types of matings. The chances range in these from 1 in 4 to 1 in 64. If these seven types occurred with the same frequency, and the 28 varieties of mating were made equally often, the chances for the Mongol to appear in the group as a whole would be 1 in 14. As there is no reason to suppose that the only combination of parents producing the Mongol is the one in which the parents are hybrid for each of the factors in question, namely, *AaBbCc*; even this combination of three recessive factors gives a higher frequency of appearance than we actually find; for it must be remembered that in choosing the conditions of 1 in 64 the combination was taken that gave the least chance of producing the defective child.

If we now take four recessive characters, and determine the chances of all four coming together in the same individual, we find first that there are 15 types of parents who could produce the desired combination of characters, and these might be grouped in 120 different combinations. Here the chances range from 1 to 4 in ten of the matings to 1 to 256 in one of the matings. Again, assuming that all 120 matings are made with the same frequency, the chances that the Mongol would appear in these families would be 1 in 30.

If we now choose five recessive factors as the basis of the defect, we find that there are 31 possible types of parents, all normal themselves, but capable of producing the desired combination of factors, *aabbccdde*. There are 486 possible combinations of these 31 types, in which the chances of having the defective child appear, range from 1 to 4 in some of them to 1 to 1024 in one. Assuming that all 486 combinations are made with the same frequency, the chances for the Mongol to appear in the group are 1 in 63.

Although this is in almost exact agreement with the conditions chosen, 1 in 64, and although these theoretical values were in close approximation to those found by dealing with the recorded cases of Mongolism, it is apparent how impossible it is to say that this defect is due to a combination of five recessive factors. We do not know the genetic constitution of the parents, and we do not know with what frequency the various combinations are made. Any deviation from the equality in number of all types of parents that was at the basis of the estimations made above would of course cause the chances of the Mongol appearing either to be much less or much greater than the number given. Such theoretical considerations, however, although not affording any proof of the mode of inheritance of Mongolism, do bring very clearly before us an explanation of how a condition dependent upon a number of factors, can be so infrequent in most families, that it appears only as isolated cases, while in other families it may affect as many as four out of ten children (90). In such an instance, each parent would have almost the entire combination of factors present in his germ cells, but be saved from being a Mongol himself by the presence of one of the factors in the dominant condition, as, for example, *aabbccDdee*.

Another combination of factors which approximates these results closely is one of two dominant and four recessive factors. The affected person might be homozygous or heterozygous for one or both of the dominant factors, but homozygous for all the recessive ones. There are 140 possible types of parents, with over 8000 possible types of matings. Assuming that these matings were all made with the same frequency, the chances for the Mongolian imbecile to appear would be 1 in 70. This value is close to 1 in 63, and might explain the results found from cases in the literature as well as that based upon the assumption that the disease is due to the presence of five pairs of recessive factors.

It must not for a moment be assumed that this method of attacking the problem is looked upon as amounting to proof of any theory whatever. It is merely put forward as of interest that the theoretical values obtained are in such close agreement with those obtained by cases from the literature, both with respect to amaurotic family idiocy, which has been looked upon as due to unit recessive factors, and with respect to Mongolian idiocy which corresponds to those results obtained when the assumption was made that it was dependent upon five pairs of unit recessive factors, or two dominant and

four recessive factors. Although these theoretical considerations have not proved how Mongolism is inherited, they at least prove that it is *not* due to a pair of unit recessive factors, as has been suggested.<sup>114,115</sup>

After this paper had been prepared and was ready for publication, reference was found to Orel's papers<sup>131,130</sup> which were procured and his statistics incorporated in the text. It was found that he, too, says that Mongolian idiocy is due, not to one factor, but to a row of factors, in the germ cells.

**Conclusions.** From a survey of the literature dealing with Mongolian idiocy, I conclude that no adequate support for the contentions that syphilis, mental or physical suffering of the mother during pregnancy, advanced age of the mother at the time of conception, reproductive exhaustion due to a large number of pregnancies, or to the father being younger or much older than the mother have any etiologic significance in the production of this disease.

Evidence is presented that these and all other environmental influences that may be mentioned are not the cause of Mongolian idiocy, but that it is due to inherited defects, and so is germinal in origin.

There is no support for the statement that it is due to the presence of one pair of unit recessive factors.

Its mode of inheritance appears to be much more complex, and figures are given showing the similarity between theoretical and actual results when the theoretical are based upon the assumption that the disease is due to the simultaneous presence in the germ cell of five pairs of recessive factors or two dominant and four pairs of recessive factors, carried in as many different chromosomes. It is not, however, suggested that such agreement constitutes proof that this is the mode of inheritance of Mongolian idiocy.

**Appendix.** When a factor is spoken of in this paper as being responsible for a disease, it is not to be understood that the term "factor" is synonymous with "gene." It merely refers to that group of determiners, be they one or many, residing in one chromosome, which are responsible in whole or in part for the appearance of the particular disease in question.

Jennings has objected to the term "unit character," because he says that eye color, for example, which has been designated as a unit character, may in reality depend upon as many as 50 genes, absence of any one of which would interfere with the appearance of red eyes. Thus a fly may have 49 of the necessary genes for red eye color, but show white eyes through the lack of 1 gene. It is, therefore, not a unit character. To conceive of such complex qualities, as mental states, for example, as dependent upon a single gene or several genes is impossible, he says. This is quite true, but since there are only a limited number of chromosomes, it becomes evident that many genes are located in one chromosome. If *all* the genes responsible for the disease, let us say, are located in the *same* chromosome, then it may be termed a unit character in the sense that in the process of transmission, that disease will be passed on in the same manner that it would have been were it determined by one gene alone.

Jennings' conception that these so-called unit characters are dependent upon the presence of many genes, some of which may be lacking in one person, others lacking in another whose genetic constitution is thus differ-

ent despite their possessing the same somatic character, is of great help in the interpretation of what might otherwise seem to be irregularities in the transmission of various characters. Thus, as Jennings points out, a character that behaves as a dominant in one family may act as a recessive in another, a fact difficult to explain if the character is conceived to be due to one gene alone.

Applying this idea to the above discussion merely means that the genes, no matter what their number may be, which are responsible for the appearance of the disease known as Mongolian imbecility are probably located in as many as five or six different chromosomes. "Factor" refers merely to the group of genes which are held in one chromosome.

After this paper was prepared, a book by Brousseau and Brainard entitled "A Study of the Physical and Mental Characteristics of Mongolian Imbeciles" appeared. They reach the conclusions stated in the above paper, that none of the theories advanced as to its cause are adequate. They postulate an endocrine dysfunction in the patient himself. Heredity has no part in its production, since the family history is usually good, so they state. That endocrine disturbances may be the cause of it I admit, but if so, heredity is at the basis of the inadequate endocrine system.

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## ASTHMA DUE TO THE MAYFLY.

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THREE years ago, a patient was encountered who attributed his seasonal attacks of asthma to the annual invasion of swarms of Mayflies from Lake Erie. Upon investigation, such proved to be the case. Since our attention was first called to this condition, we have discovered three additional cases. Nowhere, have we found in the literature instances given in which insects themselves were the direct inciting cause of asthma. For this reason, we report the cases to follow and give a short description of the life habits of the Mayfly, with an explanation of the manner by which its produces asthma in susceptible persons.

**Case Reports.** CASE I.—Mr. W. H. T., aged thirty-seven years, who resides at Point Place which is on the west side of Maumee Bay, Lake Erie, was first seen on July 21, 1926. His complaint was of an asthmatic attack which had begun about July 1 and which had persisted almost continuously since. The patient stated that he formerly suffered from hay fever for some fifteen years. For the last three years, there had been no hay fever, but he had had asthma alone coincident with the annual invasion of the Mayflies from Lake Erie and lasting until they had disappeared. These annual invasions usually began about July 1 but sometimes occurred earlier. The patient further stated that he only obtained relief from his asthmatic paroxysms by going to the home of his sister in Toledo, a distance of several miles from the lake, where there were no Mayflies about.

Physical examination showed no abnormalities except the usual chest findings during an attack of bronchial asthma.

*Cutaneous Tests.* An extract was made from some dead Mayflies, using Coca's solution for the extracting fluid. By the scratch method, the patient gave a large positive reaction to this extract, the wheal measuring 2.8 cm. in diameter, with pseudopodia and a wide border of erythema. The control test was negative. Mild positive reactions were also obtained to short and giant ragweed pollens. It was noticeable that reactions to timothy, June grass and orchard grass were negative, these being the pollens prevalent in this vicinity during June and July.

*Progress of Case.* No attempt was made to desensitize the patient when he was first seen, as the swarming season for the Mayflies was nearly over. He reported again in June, 1927, with a recurrence of his asthma, having been free since August 1, 1926. He stated that his asthma began on June 17, shortly after a northeast wind had brought a swarm of Mayflies from the lake. Desensitization by means of gradually increasing doses of diluted extract was then commenced. The first injection consisted of 0.15 cc. of a 1 to 10,000 dilution, with no untoward reaction. These injections were repeated at intervals of five to seven days for the remainder of the summer. After a few doses had been given, the patient began to notice some relief and although the Mayflies swarmed at intervals until August 1, he obtained noticeable protection by the middle of July.

From September, 1927, injections of the extract were given at monthly intervals during the fall, winter and spring, the strength being gradually

increased so that a maximum dose of 0.3 cc. of a 1 to 30 solution was attained by June 1, 1928. The patient remained perfectly free from asthma during the summer of 1928 in spite of repeated exposure to the Mayflies.

CASE II.—Mrs. B. M. D., aged thirty-seven years, residing in East Toledo, first developed hay fever and asthma at the age of fifteen years and had had hay fever yearly since. In the spring of 1914, the family bought a cottage at Toledo Beach on the shore of Lake Erie. That June she had severe asthma lasting several weeks, coincident with the Mayfly invasion. She had no hay fever the remainder of the summer until late in the fall. Ever since 1914, patient had noticed that whenever she was exposed to these swarms of insects at the summer cottage she developed hay fever and asthma. For several years she has avoided going to the cottage during the swarming season and has had no symptoms until the middle of August.

By the scratch method, this patient gave marked positive reactions to short and giant ragweed. The reactions to June grass, timothy and orchard grass were negative. There was a huge positive reaction to Mayfly extract, measuring 3.5 cm. in diameter, with pseudopodia, erythema and itching.

No treatment with Mayfly extract was attempted as the patient avoided exposure by staying away from her cottage at the lake shore. Upon request, she returned for reexamination in February, 1929, when it was found that she still gave marked positive skin reactions to the ragweeds and Mayfly extract but to no other substances.

CASE III.—The following case history was contributed through the courtesy of Dr. C. E. Price of Toledo. "E. M., male, aged twenty-seven years, seen only once during July, 1928; has had hay fever symptoms for the past four years. The first year, rather mildly. The symptoms have begun about the first of July and he has noted that they develop with the arrival of the Mayflies from Lake Erie, his home being on the lake shore. With the disappearance of the flies, his symptoms have ceased and he has no such symptoms throughout the remainder of the year. He is not subject to frequent colds. In 1928 and to a lesser extent in 1927, he noted some asthmatic symptoms. He stated that on his way to Toledo, when he got farther away from the lake, his symptoms began to improve and during his stay overnight in Toledo, he had very slight obstruction to breathing and much less sneezing.

"Examination by a rhinologist gave negative findings except for typical allergic appearance of nasal mucosa. Cutaneous skin reaction to Mayfly extract gave marked positive reaction, rated at 5+. Reactions to grass pollens prevalent at this time were negative."

CASE IV.—Mr. L. H., aged thirty-six years; residence Sandusky, Ohio. Since the age of six years, he has had annual attacks of nasal obstruction, coryza, itching of eyes and mild asthma, always associated with invasions of Mayflies, lasting from about July 1 until middle of August. He has had no symptoms at any other time of year, and has never been free from symptoms any year since the trouble began.

This patient stated that his symptoms are always worst when storms from the northeast blow across Sandusky Bay bringing with them large numbers of Mayflies. Direct contact of these flies with the skin of his neck and face causes huge hives.

The scratch test with a drop of Mayfly extract gave a large positive reaction measuring 2.3 cm. in diameter with pseudopodia, erythema and itching. All other tests were negative including grasses and ragweeds. This patient was seen for the first time quite recently and is now being desensitized to Mayflies.

**The Mayflies (Ephemera).** Mayflies (lake-flies, shad-flies, June-flies, "Canadian soldiers") belong to the Order Ephemera. They are found along the shores of lakes and large rivers in various parts of the world and are especially abundant in the Great Lakes region. The Mayfly larvæ because of their aquatic existence, are of great importance as fish food in fresh-water lakes and streams. So important are these insects from an economic standpoint that the Bureau of Fisheries has sponsored investigations of their distribution and life habits. The latest and best of these reports is a study by Needham<sup>1</sup> entitled, "Burrowing Mayflies of Our Large Lakes and Streams." This study contains a complete bibliography. A more extended description of the life habits of these insects may be secured from the texts by Comstock<sup>2</sup> and by Kellogg.<sup>3</sup>

The name of this order is from the Greek word Ephemeros, "lasting but a day." It was given to these insects on account of the shortness of their lives after reaching the adult state. This order includes only a single family, the Family Ephemeridæ. There are about 300 known species of Ephemeridæ of which some 85 occur in North America.

Prof. Clarence H. Kennedy<sup>4</sup> of the Ohio State University contributes the following information regarding our local species: "The common species at Toledo which come out of the lake in such great abundance is *Hexagenia bilineata* (Fig. 1). Just before this large one appears in such great numbers, a species slightly smaller with speckled wings appears, which is *Ephemera* (Fig. 2). The large species, *Hexagenia*, has a brown stripe along the front side of the wing. About a dozen other small species occur along the Lake Erie shore, but you seldom see these more than a dozen specimens at a time."

*Life History.* In its under-water form, the Mayfly exists as a tiny six-legged creature called a nymph (Fig. 3). It has delicate fringed gills along its sides, two or three long appendages on the end of the body, and strong jaws with which to burrow and chew (Fig. 4). It can both walk and swim and lives on the bottom of shallow lakes and streams, feeding on small particles of animal or vegetable matter. This nymph crawls about; feeds, grows and undergoes frequent moults. After about the ninth moult (there may be twenty moults in all) there appear on its thorax four little sacs which are the beginning of the wings. With each moult these grow larger until finally at the end of the immature life, the nymph splits open the cuticle along the back and after hardly a second's pause the winged Mayfly emerges. The life of the nymph is from one to three years, depending on the species.

Most of the Mayfly species go through another moulting after acquiring wings. After flying a short distance, the Mayfly alights and sheds its skin again, a thin layer coming off from all parts of its body—even from its wings. The stage between the first issuance

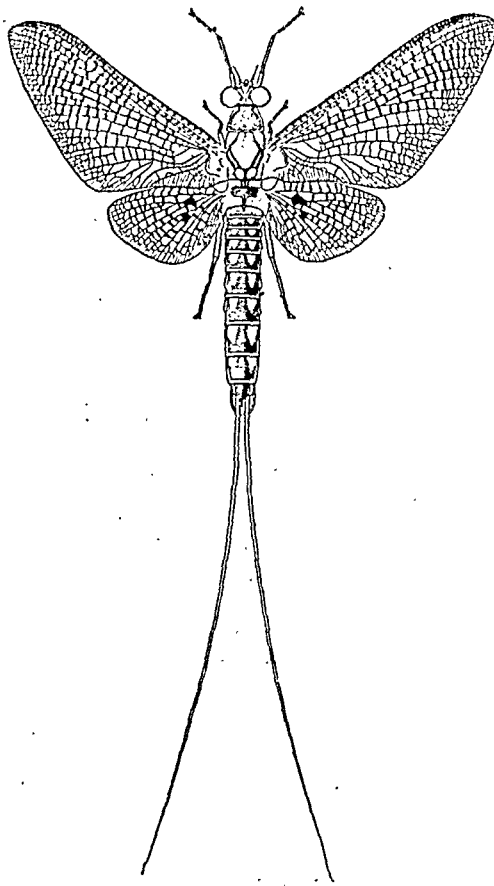


FIG. 1.—Adult male Mayfly, *Hexagenia bilineata*. (After Needham.)

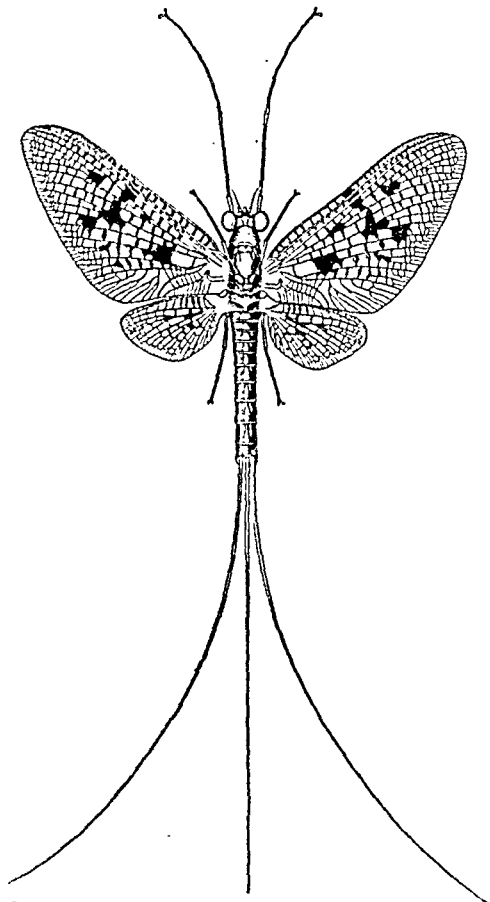


FIG. 2.—Adult male Mayfly, *Ephemera varia*. (After Needham )

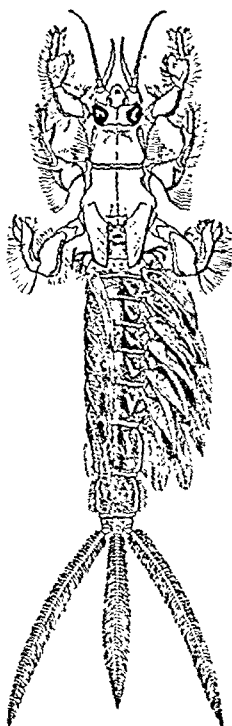


FIG. 3.—The nymph of *Hexagenia bilineata*; dorsal view. (After Needham.)

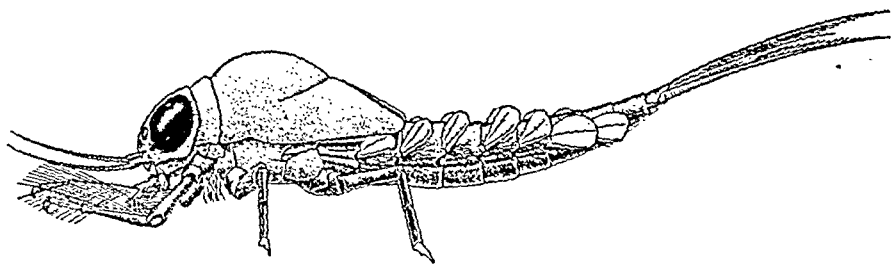


FIG. 4.—The nymph from the side. (After Needham.)

from the water with expanded wings and the final moulting is called the subimago stage and may last in various species from a few minutes to twenty-four hours.

About July first along the shores of Lake Erie, swarms of the adult Mayflies appear. They come in waves for the succeeding four to six weeks. Myriads of these insects and their shed skins may be seen clinging to the sides of buildings (Fig. 5), trees or on shrubbery near the lake shore. Sometimes the winds carry dense clouds of Mayflies far inland. Pavements are often made slippery by their dead bodies which may accumulate to a depth of several inches. Sometimes the great swarms fall to the waters surface and are finally cast up on the beach in thick windrows, miles long.

The flying dance is the most conspicuous event in the life of the fully-developed, winged Mayfly and indeed makes up nearly all of

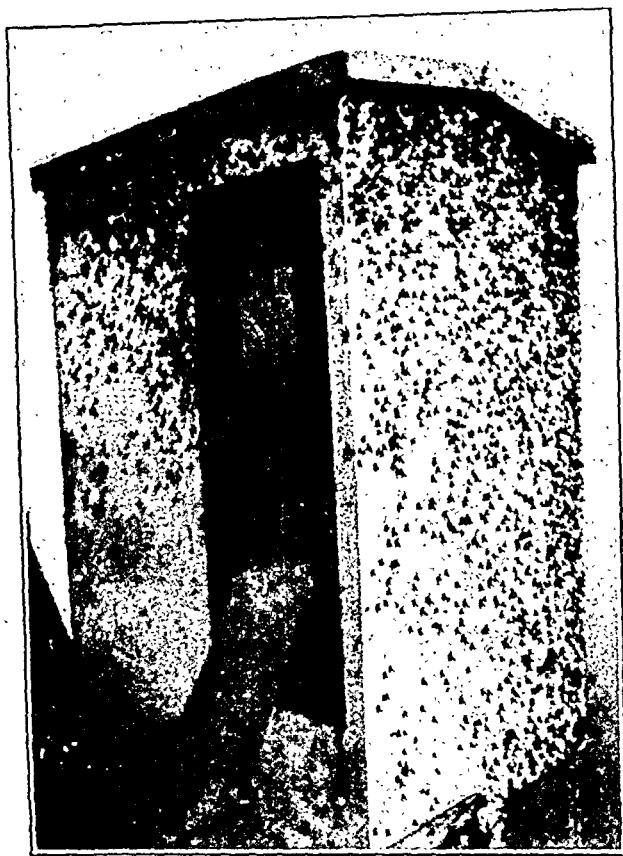


FIG. 5.—Mayflies on side of building. (After Needham.)

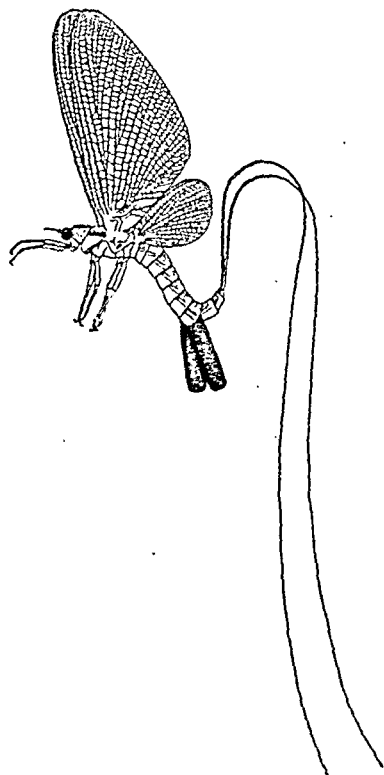


FIG. 6.—Adult female, hovering with egg packets extruding. (After Needham.)



it, for owing to the lack of suitable mouth parts with which to take food, the winged adult lives but a few hours. It has but one duty to perform in its brief life in the air: to reproduce its kind. In the early twilight, the fly comes forth full fledged, joins its thousands of issuing companions, mates, drops its masses of eggs (Fig. 6) onto the lakes surface and soon flutters and falls after the eggs. From each egg dropped on the water, hatches a nymph to perpetuate the species.

**Discussion.** When the patient described under Case I was first encountered, we were at a loss to account for the relation between the swarming of the Mayflies and this man's asthma. The Mayfly gives off no emanation. Its wings and body are formed of a chitinous material and the shaking of a large number of the dead insects in a glass jar, produced no dust. Furthermore, the dead insects when decomposed, are reduced to an oily mass which obviously cannot be wind-borne. It was only when we learned of the final moulting of the Mayfly after its emergence from the water and the shedding of its skin after the subimago stage that the mode of production of the asthmatic paroxysms was clear. This shed skin is very thin and delicate and upon close observation when the Mayflies are swarming, fragments of it may be seen adhering to walls, posts, trees etc., where it has been deposited. Particles of the shed skin are readily wind-borne and when one considers the millions of insects which take part in the annual Mayfly invasion, it is not difficult to obtain some comprehension of the amount of allergenic material given off by these insects. As had been described the Mayflies are piled up in long windrows on the lake beach and they accumulate by the ton along the streets of lakeside towns. These piles of decomposing insects give off a strong "fishy" odor, and their composition no doubt resembles that of fish because of their long aquatic existence. To those familiar with the ability of fish proteins to cause asthma in specifically sensitized individuals it will be readily understood how the shed skin of the Mayfly can be a potent cause of asthma in those who have become sensitized to it from long exposure, year after year.

It should be stated that since 1927 we have used the Mayfly extract routinely in our skin tests. In several hundred cases, the four above reported were the only ones to give definitely positive reactions. This we regard as further corroboration of the specific sensitization of these four patients to some substance in the shed pellicle of the Mayfly.

**Summary.** 1. Four cases of asthma due to Mayflies have been reported.

2. The asthma has been caused by the inhalation of minute particles of the shed pellicle of these insects.

3. One patient has been successfully treated both preseasonally and coseasonally with an extract made from dried Mayflies.

4. Use of Mayfly extract routinely in skin tests on several hundred patients has given positive reactions in only the four cases cited.

5. Attention is called to the widespread distribution of these insects in rivers and fresh-water lakes throughout the world, and the possibility of their being sensitizing agents.

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### A CLINICOPHYSIOLOGIC STUDY OF THE PATHWAY OF PAIN IMPULSES IN CARDIAC DISEASE.

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**Introduction.** In a former contribution,<sup>1</sup> a report was made on the clinical results obtained in the relief of cardiac pain by means of paravertebral alcohol block. Observations were then made as to the pathway that these pain impulses took from the heart to the spinal cord before passing into the spinothalamic tracts to be transported by these pain conveying tracts to the diencephalon. At that time the examinations made suggested that the pathway along which these pain impulses traveled from the *situs* of origin, the heart, was through the stellate ganglion as well as through those rami communicantes and spinal ganglia which were found to extend from the eighth cervical down to the sixth and seventh thoracic (C 8 to D 7), before they entered into the spinal cord to be conveyed *via* the spinothalamic tracts to the thalamus, as pain. In a recent article by Ionescu,<sup>2</sup> experimental observations were made on animals, which confirmed these previously observed clinical evidences, thus tending to confine the afferent sensory pathway from the heart to those rami communicantes and spinal ganglia found between the eighth cervical (C 8) and the seventh thoracic (D 7) ganglia. This paper is presented to correlate these previously made clinical findings with the subsequently independently-made observations on animals in order to establish more firmly the pathway for cardiac pain.

**Anatomical Pathways of the Afferent Cardiac Nervous System.** The following description presents the anatomy of the cardio-afferent nervous system:

The cardiac plexus is brought into contact with the sympathetic system through three cardiac nerves, that is, the superior, middle

and inferior cervical cardiac nerves. These nerves originate from the superior, middle and inferior cervical ganglia. The right superior cervical nerve enters the deep cardiac plexus and gives off a few branches to the anterior surface of the aorta. The left superior cervical cardiac nerve joins the superficial cardiac plexus. It is of importance to note that the superior cardiac nerve communicates freely with the middle cardiac nerve and with the superior cervical cardiac branch of the vagus. The middle cervical cardiac nerve arises from the middle cervical ganglion. Often this nerve and ganglion are entirely absent. Both the right and left middle cervical cardiac nerves end in the deep cardiac plexus. The middle cervical cardiac nerve anastomoses in the neck with the superior cervical cardiac nerve and the inferior laryngeal nerve of the vagus. The inferior cervical nerve arises from the inferior cervical ganglion and at times from the first thoracic ganglion. It anastomoses with the middle cervical cardiac nerve and the inferior cardiac nerve. The lowest cardiac nerve terminates in the deep cardiac plexus while the vagus nerve also ends in the deep cardiac plexus. The nerves of the heart are derived from the cardiac plexus. These nerves pass down along the aorta and are distributed to the auricles. From there they accompany the coronary arteries along the auriculo-ventricular groove thus forming the coronary plexus. From this plexus, branches are given off to the ventricles. The ascending aorta has nerve fibers which are in relationship through the rami communicantes with the first six spinal thoracic segments.

There is some question as to whether the afferent fibers of the inferior cardiac nerve pass to the fourth, fifth, sixth and seventh cervical nerves. There is evidence to the contrary. First, clinically, it is rare for pain to appear over the dermatomic segments supplied by the fourth, fifth, sixth and seventh cervical roots. Embryologically the evidence is also against this occurrence. Afferent fibers from the heart enter the upper cervical and thoracic segments which extend from the first to the seventh dorsal segments. Apparently, in the development, the fibers going to the lower cervical nerves are not developed from the inferior cardiac nerves. All three cardiac nerves convey motor impulses to the cardiac plexus. Ranson maintains that most or all of the constrictor fibers to the aorta and coronary vessels come through the superior cardiac nerve. The sensory afferent impulses from the middle and inferior cardiac nerves reach the spinal cord through the rami communicantes. They enter into the thoracic segments, extending from the first to the seventh segments. These sensory afferent fibers pass into the central nervous system by way of the rami communicantes into the upper thoracic segments. Hypothetical nerves, such as a special depressor nerve and the vertebral nerve and structures seen in comparative anatomic studies but not established for human beings, are omitted in this discussion.

**Clinical Evidence Concerning the Pathway of Cardiac Pain as Ascertained by the Subjective Radiation Complained of by the Patients.** Irrespective of the place of origin of those painful stimuli which give rise to cardiac pain, and of the nerves through which they pass, these impulses must ultimately pass into the spinal cord or brain stem to travel by way of the spinothalamic tracts in the spinal cord to the thalamus and thus ultimately reach the sphere of consciousness. Before entering the spinal cord however, these pain impulses, as with any pain impulses, must first enter the dorsal-root ganglia so as to give rise to the phenomenon of referred pain. It is upon these basic physiologic principles that these subjective pain areas, as complained of by the patients are explained. Of further interest, are the observations, that the areas complained of are parts of the body surface relegated in nearly all of the cases to dermatomic segments that are supplied by those spinal nerves found between the eighth cervical and seventh thoracic segments. In a careful examination of the histories personally taken, as well as a perusal of the literature of many cases of pain due to angina pectoris, coronary disease and aortalgia, one is quite forcibly struck with the fact that the radiation of pain is relegated quite consistently to those areas of the body supplied by the eighth cervical down to the sixth or seventh dorsal (C 8 to-D 7) nerves. These observations also revealed that any part or all of the chest may be subjectively referred to as the seat of the pain. Although it is true that at times the patients complain of pain in the back of the head (C 1-2) or in the ear (C 2) and at times in the lower jaw (trigeminal), yet it is worthy to note, that these two former sites are of rare occurrence while the last site is indeed a curiosity. A complaint of pain along the outside of the arm, which is supplied by the fourth, fifth, sixth and seventh cervical nerves is of such rare occurrence, that its actual existence is greatly to be doubted. In fact, anatomically, it is quite likely that no afferent sensory fibers of the inferior cardiac nerve pass through these four latter cervical nerves. Embryological studies also seem to support this conclusion. Therefore, from a clinical point of view as ascertained by the subjective complaints of the patients, we can logically say, that the impulses, which produced pain passed through dorsal root ganglia which supplied those dermatomic segments innervated by nerves emerging from between the eighth cervical and seventh dorsal spinal segments.

**Clinical Evidence Concerning the Pathway of Cardiac Pain as Ascertained by the Neurologic Examination of the Patients. (Head Zones.)** As stated, all sensory impulses, which are conveyed by nerve fibers from an organ, must first enter into dorsal root ganglia before entering the spinal cord to be conveyed by the spinothalamic tracts to the sensorium. The spinothalamic fibers transmitting

these stimuli arborize about cells in the dorsal root ganglia known as Dogiel cells. The constant bombardment of these somæ by discharges coming from a diseased organ produce in these cells a state of hyperirritability. When a sensitive dermatome, which is supplied by such an irritable cell, is roused by any physical agent, that is, pin prick, heat, cold—a painful response ensues. We thus see that this method of investigation is of great value in ferreting out those ganglia which are the recipients of the continuous stream of painful impulses from the diseased organ. Simply stated, this method reveals the pathway along which the painful influences are traversing so as to enter the spinal cord. Based upon these neurophysiologic facts, careful epicritic and protopathic tests were performed. In the 8 cases originally reported and 12 cases to be reported, definite sensory changes were observed over the skin. In all cases the protopathic skin tests clearly gave proof of the hypersensitiveness of the skin. Those zones of hyperirritability were limited to areas of the skin supplied by those peripheral nerves which emerge from between the eighth cervical down to the seventh thoracic spinal segments. Again, it is of value to note, that the neurologic examination failed to elicit Head Zones over the back of the head (C 1-2) or over the lower jaw (trigeminal nerve). The investigation also failed to reveal any hypersensitiveness of the skin to these tests over the radial aspect of the upper extremities (C 4-5-6-7).

This method, therefore, also seems logically to suggest that the discharges of pain from the heart pass *via* those sympathetic fibers and dorsal root ganglia that are emerging between the eighth cervical and seventh dorsal (C 8 to D 7) spinal segments.

**Operative Evidences as to the Pathway of Cardiac Pain as Ascertained from the Various Procedures Performed.** In reviewing the various operative measures instituted for the amelioration of the severe pain incident to cardiac disease, data were also elicited which clearly indicated what was not the pathway of pain from the heart. Nevertheless, these failures in the several surgical attempts to relieve the pain are of invaluable importance in indicating the correct pathways. Since the original suggestion of cervical sympathectomy by François Franck and the first actual surgical interference for the relief of angina pectoris by Jonnesco, of Bucharest, in 1916,<sup>3</sup> surgeons have attempted to relieve the agonizing pain incident to the cardiovascular disturbance. That the surgical attempts are based on insufficient and inadequate anatomic, physiologic and pathologic evidence is amply borne out by the great variety of surgical procedures attempted. The various surgical operations will be reviewed and discussed briefly, so that a clearer understanding may be obtained as to the significance of the information elicited, thus aiding in the disclosure of the correct pathway for cardiac pain.

1. Method of Jonnesco. By this method the entire cervical chain, along with the first thoracic ganglion, was extirpated (Fig. 1). Danielopolu objected to this method. He contended that this operation severed the vasomotor fibers to the coronary arteries as well as the vasoconstrictor fibers to the lung. These objections were answered by Jonnesco in a recent article. He asserted that physiologists, supported by extensive experimentation, are of the opinion that the sympathetics are vasoconstrictors. Hence the removal of the sympathetics does not impair the efficiency of the coronaries but, in fact, augments it.

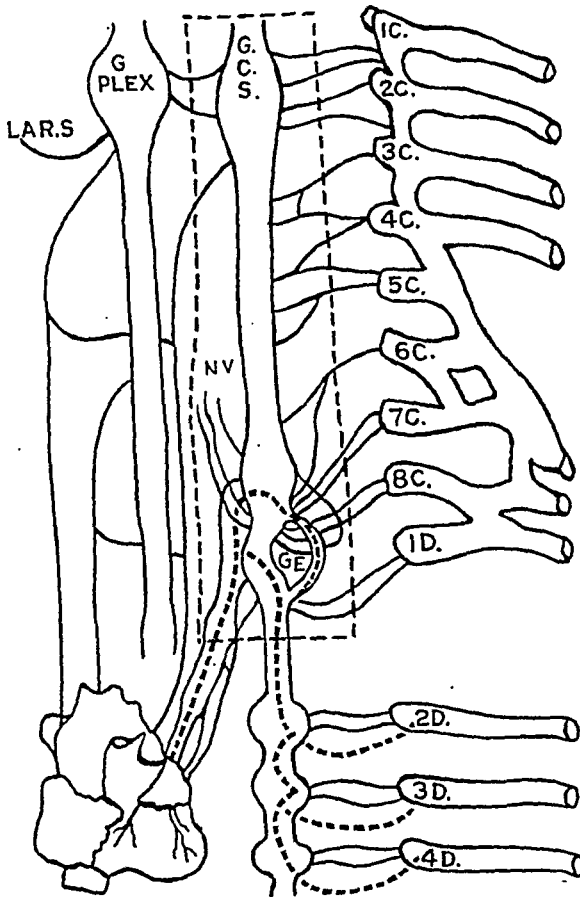


FIG. 1.—(After Danielopolu.)

2. Method of Danielopolu and Hristide.<sup>4</sup> These operators sectioned the cervical sympathetic cord on the left side above the stellate ganglion (Fig. 2). Along with this section, the spinal ganglia of the spinal nerves on the left side were injected with alcohol. At that time the operators were not ready as yet to report the value of this method.

3. Method of Danielopolu. (A) On January 1, 1924, this surgeon reported that Gino Pieri of Bellino was the first to follow the operator's new method. He sectioned the cervical sympathetic

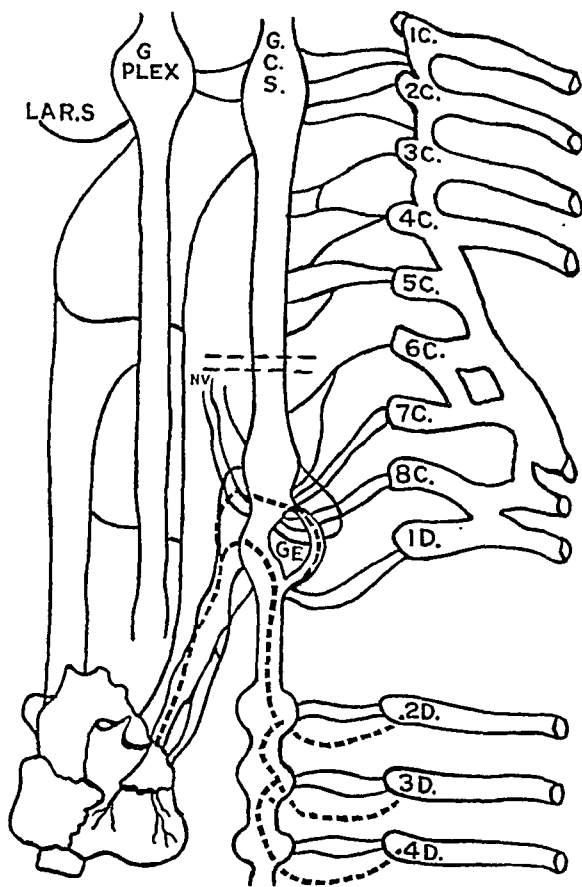


FIG. 2.—(After Danielopolu.)

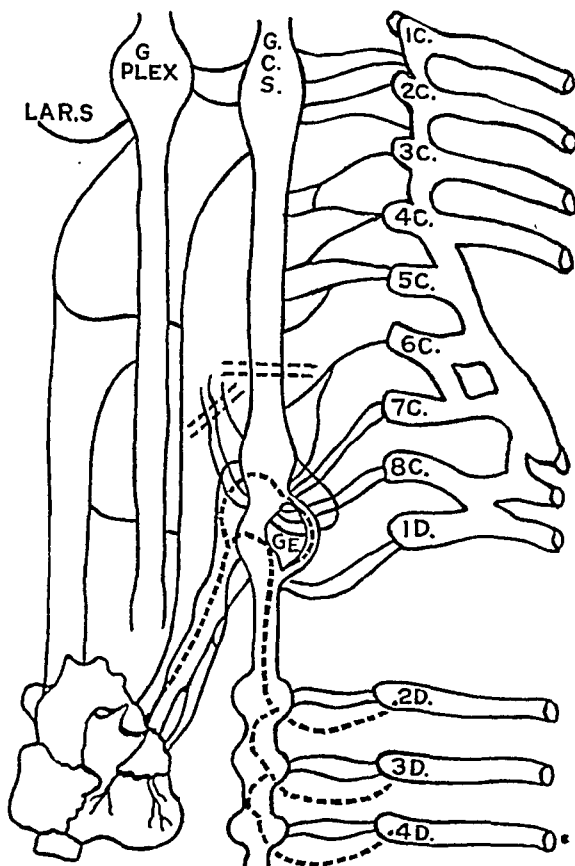


FIG. 3.—(After Danielopolu.)

chain above the stellate ganglion, together with the vertebral nerve, as well as a nerve which joins the superior cervical ganglion to the cranial nerves (Fig. 3). The immediate results were good. No report as to the condition of the patient at a later date was given. (B) In October, 1924, Danielopolu reported resection of the sympathetic cervical chain without removal of the inferior cervical ganglion and the first thoracic ganglion (Fig. 4). In addition he sectioned the vertebral nerve and the branches of the vagus, which were about to enter the thorax. (C) In a less complete operation the

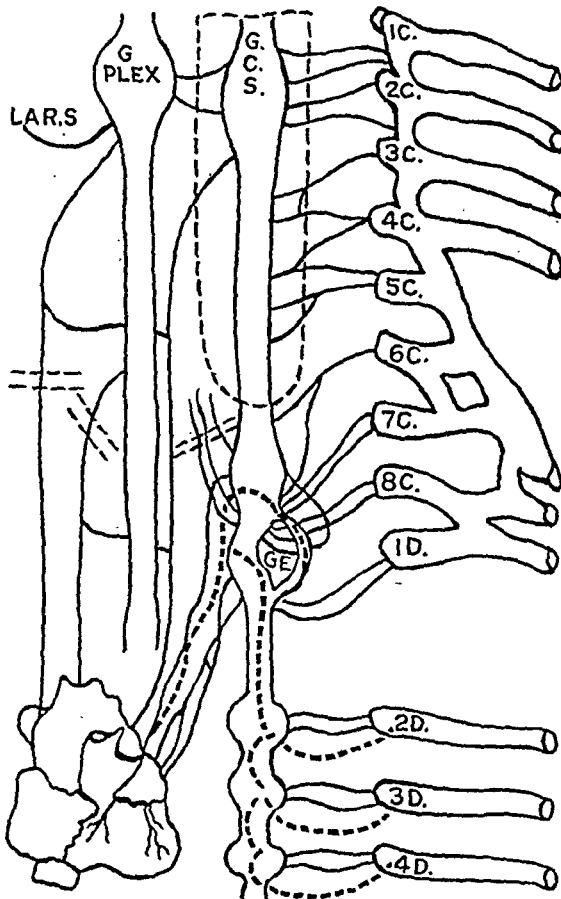


FIG. 4—(After Danielopolu.)

superior and middle cervical ganglia were extirpated on one or both sides (Fig. 5). In January, 1925, Lilienthal<sup>5</sup> reported three such cases with good results. (D) In February, 1925, the following operation was performed by Danielopolu: the cervical sympathetic chain was resected. The inferior cervical ganglia, as well as the first thoracic ganglia, were left intact. The vertebral nerve was sectioned. All branches leaving the vagus to enter the thorax were severed. The rami communicantes, which joined the inferior cervical ganglion and the first thoracic ganglion to the last pair of cervical nerves, were severed (Fig. 6). In addition to the above



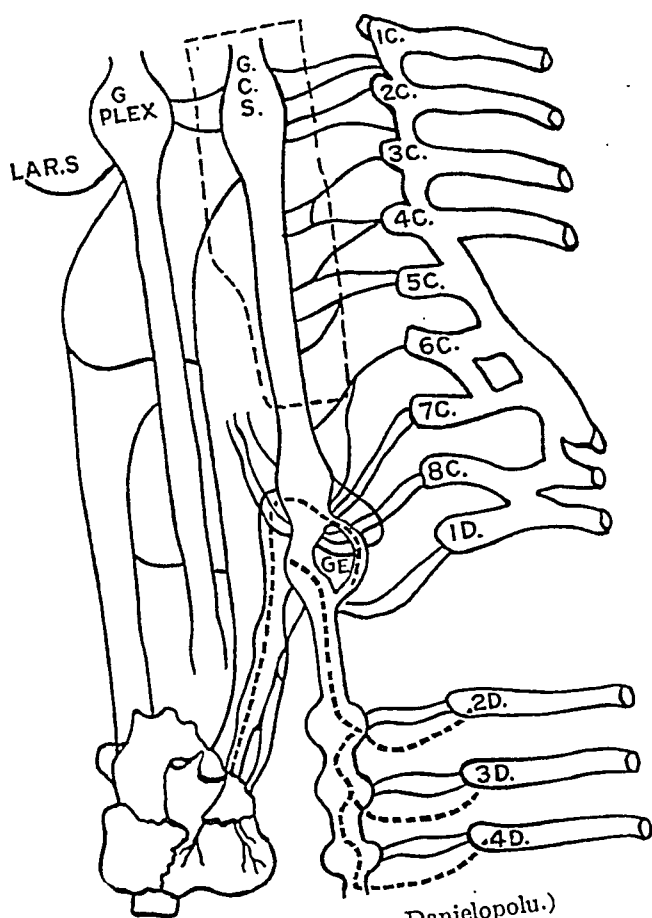


FIG. 5.—(After Danielopolu.)

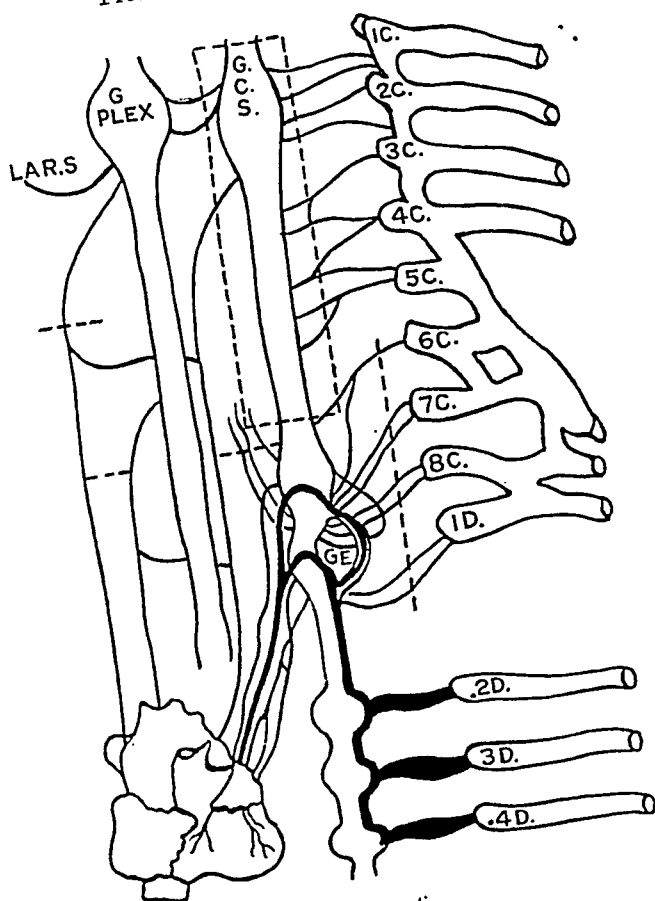


FIG. 6

operations, Eppinger and Hoffer sectioned the so-called depressor nerve, while Coffey and Brown severed the cervical sympathetics, together with the superior cardiac nerve on the left side. Hoffer in four cases of angina pectoris dissected the vagus nerve without influencing the severity of the pain.

The résumé of these various operations shows quite suggestively, that if pain impulses do pass through the middle, superior cervical ganglia and vagus they do so in a very minor degree. These observations are quite supported by the animal experimentations to be later discussed as well as by the results obtained by the paravertebral alcohol nerve block.

**Evidence as to the Pathway of Cardiac Pain Elicited by Means of the Paravertebral Block.** In a former contribution, a report of 8 cases suffering from cardiac pain was made showing the results obtained by destroying the rami communicantes and dorsal-root ganglia conveying impulses of pain from the heart. In addition to the former report, data, not as yet reported, will be incorporated here as well as 12 additional cases treated by the writer. In these 12 cases gratifying results were obtained in all but 2 cases. In a recent paper from the Massachusetts General Hospital<sup>6</sup> 5 additional cases were reported in great detail in which the alcohol paravertebral alcohol block was used with admirable results. Mandl<sup>7</sup> also reported 16 cases treated by this method with excellent results. This discussion, therefore, is based on a total of 41 cases, treated independently by three different operators. This method is of invaluable aid in the study of the route taken by these impulses which incite the perception of cardiac pain, in that we destroy nerve fibers and then observe what ensues to the complaint of pain as personally expressed by those treated. The following theoretical principles are of value in understanding the paravertebral alcohol block as a method in studying the course of cardiac pain. As previously stated, the cardiac pain was referred subjectively to the surface of the body supplied by part or all of the nerves coming forth from between the eighth cervical down to the seventh thoracic nerves (C 8 to D 7), and again, as formerly set forth, these very same skin segments were the ones which were sensitive to skin tests. The conclusion was quite evident, that if these irritable ganglia or sympathetic fibers, which came to the ganglia from the heart loaded with pain impulses were destroyed, and if pain, as a result of the destruction, disappeared, the pathway of cardiac pain to a great extent would be solved. In light of the fact that an 80 per cent solution of alcohol destroys myelin and since the afferent sympathetic fibers are finely myelinated, a paravertebral alcohol block was performed, injecting each of the irritated ganglia. As a result of the injection into the nerve tissue, a typical Wallerian degeneration was produced: In all of the cases, the paravertebral injections were confined to those ganglia found between the eighth cervical and seventh thoracic (C 8 to D 7) spinal segments. The

analysis of the 41 cases showed that those treated were mostly far-advanced patients of heart disease, who suffered because of the persistent agonizing pain—that they all received a paravertebral alcohol injection into some or all of the dorsal root ganglia and rami communicantes which extended between the eighth cervical and seventh dorsal (C 8 to D 7) spinal segments—that, except for 4 cases, they were all relieved to a marked degree. Since the cardiac pain was relieved by the destruction by alcohol of the irritated ganglia found between the eighth cervical and seventh thoracic, we can reasonably say that the impulses of pain were intercepted by the alcoholic destruction of the nerves before they were able to enter the spinal cord, and since only nerves found between the eighth cervical and seventh thoracic were so destroyed, the conclusion naturally follows, that the pathway of pain is through those rami communicantes and dorsal-root ganglia found between the eighth cervical and seventh dorsal (C 8 to D 7) spinal segments.

**Evidence Elicited by Means of Animal Experimentation as to the Pathway for Cardiac Pain.** In a recent paper by D. Ionescu, experimental observations were made upon dogs and cats as to the course taken by discharges capable of producing cardiac pain. His experiences support the same conclusions as were arrived at through our clinical studies upon human beings. The following is a résumé of the method used by the experimenter and the interpretation of the results as made by him. The experiment may be divided into four steps.

*Step I.* Upon the pericardium or epicardium being pinched or pulled, or on the application of a 10 per cent solution of ammonium or barium chlorid to the left ventricle or on making a similar chemical application to the adventitia of the left coronary artery or aorta, definite manifestations of pain reactions upon the part of the animals were seen, that is, marked movements of defence, increased respirations, rise in the blood pressure.

*Step II.* The next step of the experiment was to sever on the left side the rami communicantes of the eighth cervical and the first thoracic (C 8 to D1) as well as the rami communicantes of the thoracic sympathetic chain down to the sixth ganglion. The first thoracic ganglion was not removed so as to permit its continuity with the cervical sympathetic chain and the vertebral nerve. With this section accomplished, there remained the following routes for the transmission of pain impulses from the left heart—the vagus with its depressor branch, the superior cardiac nerve, the cervical part of the sympathetic ganglionated chain, the vertebral nerve. Again the epicardium and pericardium, the left coronary artery and aorta were stimulated as was done in Step I and none of the reactions of pain as already described appeared in the animal. However, stimulating the right ventricle, a display of pain reactions were again elicited though mild in nature. No evidences of pain resulted at

all when the aorta was stimulated, even though the nerve structures were preserved on the right side.

*Step III.* The next step was to resect on the right side the rami communicantes, which extended from the eighth cervical down to the sixth thoracic (C 8 to D 6). The application of the physical and chemical stimuli to the left or right ventricle, coronary artery or aorta roused no pain manifestations. This absence of pain is observed even though the vagus nerve, the depressor nerve, the superior cardiac nerve, the vertebral nerve and the cervical sympathetic chain are left unmolested.

*Step IV.* In other experiments as carried out in man, the same operator stimulated the cranial end of the sympathetic chain but no pain was produced.

Additional evidence was brought by Schittenhelm and Kappis to the effect, that the cervical sympathetic chain does not transport pain discharges from the heart and the aorta. They observed attack of angina pectoris during an operation. They immediately injected novocain into the trunk of the cervical sympathetic chain with no relief ensuing, while upon injecting the stellate ganglion, there was at once a suppression of the pain. In an earlier paper, D. Ionescu showed that the electrical stimulation of the cranial end of the vagus nerve as well as the depressor nerve or vertebral nerve, when found in man, incited no pain reactions. Hoffer noticed in 4 cases of angina pectoris no influence upon the pain by severing the vagi. D. Ionescu pinched and pulled upon the vagus nerve without inducing pain evidences in the animals experimented upon. The experiments of Ionescu, together with the work of Hoffer, Schittenhelm and Kappis lead to the conclusion, that the impulses of pain pass from the heart through the stellate ganglion (C 8 and D 1) as well as those rami communicantes that are found between the eighth cervical and sixth thoracic spinal segments.

**Case Reports.** The first three cases are from the Medical Division, Montefiore Hospital, service of Dr. B. S. Oppenheimer.

**CASE I.**—The patient, R. C., a young female, aged twenty years, suffered from aortitis and aortic insufficiency caused by congenital syphilis. Her complaints of pain began April, 1923. In the very beginning the pain appeared over the precordium. In a few months the discomfort extended to the left shoulder blade, down the left arm and the back of the chest on the left side. The arm pain was sticking and constricting in character and was especially bad during the night. After April 17, 1924, the pain became much more severe. The attacks consisted of paroxysms of severe sticking pains lasting a few minutes and leaving in their wake a dull ache over the same area. These paroxysms were brought on with only slight exercise, and, as a result, greatly curtailed her physical activities.

She received a course of salvarsan and mercury salicylate (which was completed October 2, 1924), potassium iodid (which was discontinued several months ago), and a series of injections of Bismogenol. Following this series of treatments, she was slightly more comfortable, but the pain still persisted.

A paravertebral alcoholic injection was performed April 23, 1925. After the injection into the fourth, fifth, sixth and seventh dorsal roots on the left side, the patient was almost completely relieved of pain and in addition was able to carry on increased physical activity to exhaustion without attacks of pain. For example, before the injection of alcohol she was unable to walk more than one block without developing sharp, excruciating, sticking pain over the left chest anteriorly and posteriorly, with radiation to the left arm as far down as the hand. The pain was so severe that she was forced to stop, the distress lasting two to three minutes at a time. At present, she is able to walk from five to ten blocks, and, although she at times develops pain, she asserts that it is so mild and fleeting that she pays but little attention to it. Previous to the alcoholic injection she found that on attempting to practise on the piano for more than ten to fifteen minutes, she would be forced to stop because of the agonizing pain. Now she is able to play for at least one hour and at times more. Only occasionally has she a short fleeting pain over the left precordium. The following are the sensory changes observed before and after the injection.

April 22, 1925. Before the injection (Fig. 8).

A. Epicritic sensibilities. (1) Hyperesthesia to light touch with cotton wool extended from the third to the seventh dorsal nerves on the left side anteriorly and posteriorly. (2) She was able to discriminate temperatures ranging between 20 and 38° C. over the same region. (3) Cutaneous localization was well performed.

B. Protopathic sensibilities. (1) A zone of hyperalgesia to pin prick extended from the third to the seventh dorsal nerves on the left side. (2) A marked hyperthermalgesia was observed on the left side of the chest to temperatures above 45° and below 20° C., when compared to the right side. She was able to recognize these extreme differences in degrees on the left side.

June 1, 1925, thirty-nine days after the injection.

A. Epicritic sensibilities. (1) A zone of hypesthesia to light touch with cotton wool extended from the third to the seventh dorsal nerves on the left side. In fact, she hardly perceived the stroke of the cotton wool. (2) She was definitely unable to discriminate over the injected segments, temperatures ranging from 26 to 38° C. (3) Cutaneous localization was greatly impaired.

B. Protopathic sensibilities. (1) An area of hypalgesia to pin prick extended from the third to the seventh dorsal nerves on the left side. (2) A marked hypothermalgesia was found on the left side extending from the third to the seventh dorsal nerves, when compared with the right side. There was noticed great impairment in her ability to discriminate between extremes of temperature on the left side, that is, between 20° and above 45° C.

*Case Summary.* (1) Before injection a zone of dermatomic irritability extended from the third to the seventh dorsal nerves on the left side. Sensory examination thirty-nine days after the injection showed that the nerve conductivity was greatly reduced. (2) She had been free from pain for four months when she was discharged from the hospital. On October 25, 1925, approximately twenty-six weeks later, we received a letter from her in which she reported that she is able to walk as far as a mile without the appearance of pain.

CASE II.—The patient, F. S., a male, aged sixty-three years, suffered from angina pectoris, due to coronary disease. Fifteen months before admission, he complained for the first time of a severe, boring, retrosternal pain which penetrated anteroposteriorly. Frequently he observed that the pain was burning in nature, simulating "a feeling of hot sand." At times it was so excruciating as to induce crying. The pain would persist for twenty to twenty-five minutes, requiring morphin for its control. He

could walk no further than three blocks at a time, for, if he did, agonizing pain ensued. Twice this necessitated his being taken from the street to a hospital in an ambulance. Inhalation of amyl nitrite often relieved his attacks. Several months ago he felt for the first time slight burning paresthesia down the left upper extremity.

On June 25, 1925, he received a paravertebral injection of alcohol into the third, fourth, fifth and seventh intercostal nerves on the left side. Five cubic centimeters of 80 per cent alcohol solution were used in each dorsal root. Following this form of treatment the pains were completely relieved within twenty-four hours. There was practically no limit to his ability to walk. He was up and about most of the day, doing errands in the hospital, and he definitely asserted that he was relieved of his pain. Nevertheless, shortness of breath, when he exerted himself unduly, was a very prominent symptom. A sensory examination was done before and after the injection.

June 23, 1925, before the injection.

A. Epicritic sensibilities. (1) A zone of hyperesthesia to light stroking with cotton wool was found over the skin supplied by the second to the eighth dorsal nerves on the left side both anteriorly and posteriorly. (2) No disturbance was observed in his ability to discriminate temperatures ranging between 20 and 38° C. He had no difficulty in locating areas lightly touched.

B. Protopathic sensibilities. (1) An area of skin hyperalgesia to pin prick extended from the second to the eighth dorsal nerves on the left side. (2) An extreme hyperthermalgesia was present on the left side when compared with the right side. He was able to distinguish these extremes of temperature on the left side.

March 3, 1926, three hundred and thirteen days after injection.

A. Epicritic sensibilities. (1) When stroked lightly with cotton wool over the dermatomic segments supplied by the injected nerves, the patient hardly perceived being touched. (2) He was unable to discriminate temperatures ranging between 20 and 38° C. (3) Cutaneous localization was completely lost.

B. Protopathic sensibilities. (1) The patient observed that he could not feel the pricking of a pin over the areas of the skin supplied by the injected nerves. He experienced a peculiar dysesthesia, as he put it, "dull and frozen," when a pin was drawn across the skin. (2) His inability to discriminate the extremes of temperature was quite marked. There was, in fact, an almost complete analgesia.

*Case Summary.* (1) Before injection, a dermatomic zone of irritability was delineated. This extended on the left side over the skin supplied by the second to the eighth dorsal nerves. Three hundred and thirteen days after the injection, a sensory examination indicated that the nerve conductivity was greatly decreased. (2) He was completely relieved of all pain for a period of four months when it again appeared. He was reinjected, this time blocking the first, second, third and fourth dorsal-root ganglia and rami communicantes. Before the second injection the level of root hyperirritability was from the first to the third dorsal-root segments. Following the injection signs of diminished conductivity were noted. He is now again comfortable and free from all pain. He complains, however, of a pressing sensation over his shoulders when he attempts to rise from a sitting position, as well as of retrosternal pressure. He has now been relieved for a little more than ten months.

CASE III.—This patient, Y. S., a female, aged eighteen years, suffered from mitral stenosis and insufficiency, together with cardiac decompensation. Fifteen months before admission she developed precordial pain for the first time. She described it as sticking in character lasting from a few

minutes to as long as an hour. At times the attacks of pain would appear during the night, awakening her from sleep. She complained that with the sticking pain there was a burning sensation in the skin. These attacks would appear for a few successive days and then disappear, only to reappear. For four months preceding the treatment, however, the pain had been persistent, always more or less severe. During the ten days before injection the agony was especially disturbing, being both sticking and constricting in type, with no remission either by day or night. The pain was particularly severe in the left interscapular region, preventing her from reclining on her back. On June 25, 1925, 4 cc. of a 60 per cent alcohol solution were injected into the third, fifth, seventh and ninth dorsal roots. After the injection she experienced precordial pain only occasionally and that which she did feel was slight and fleeting in character. She was able to recline on her back without pain or discomfort over the precordium. Within one week of the injection she observed a peculiar itching paresthesia over the site of the injection. On scratching it she noted that there was very little sensation induced on rubbing the skin.

The following is a summary of the sensory findings before and after the injection.

June 23, 1925, before the injection.

A. Epicritic sensibilities. (1) The dermatomic skin areas extending from the third to the eighth dorsal nerves on the left side both anteriorly and posteriorly showed a marked hyperesthesia. She noticed that light stroking with cotton wool induced an unpleasant scratching sensation. (2) Her ability to discriminate temperatures varying between 20 and 38° C. was normal. (3) Cutaneous localization was well performed.

B. Protopathic sensibilities. (1) A dermatomic zone of hyperalgesia extended from the third to the eighth dorsal nerves on the left side. (2) In the same dermatomic zone hyperthermalgesia was observed when compared with the right side. Temperatures below 20° and above 45° C. were used. There was no disturbance in her ability to recognize extreme temperatures on the left side.

September 11, 1925, seventy-eight days after the injection.

A. Epicritic sensibilities. (1) There was no disturbance in her ability to feel the light touch of cotton wool. (2) There was no disturbance in her ability to discriminate temperatures ranging between 20° and 30° C. (3) Cutaneous sensibility was found to be unimpaired.

B. Protopathic sensibilities. (1) Her reaction to pin prick on the left side was only slightly below normal. (2) Her ability to discriminate on the left side between extremes of temperature, that is, below 20° and above 45° C., was greatly impaired. When compared with the right side there was a definite hypothermalgesia.

*Case Summary.* (1) This patient was injected with a weaker alcohol solution, that is, 60 per cent. (2) The sensory findings after the injection showed the conductivity of dorsal nerves to be only slightly decreased as compared with the previous 2 cases in which an 80 per cent solution was injected. (3) She was free from all pain for fourteen weeks, finally died from cardiac decompensation.

CASE IV.—The following patient is from the Neurological Division, Montefiore, Dr. S. P. Goodhart, chief of Division.

The patient, J. W., a male aged sixty-one years, suffering from angina pectoris associated with coronary disease and cerebral thrombosis, has for the past four years been complaining bitterly of precordial pain. At first the distress was brought on by walking two blocks, this causing such pain that he had to pause to rest. As time passed, he observed that walking even much shorter distances induced pain. He described this pain as stick-

ing, tearing, and at times constricting in character. These attacks would appear two or three times daily, each lasting from twenty to thirty minutes. For the past eighteen months he has been unable to walk more than twenty yards because of the induced agony. Every morning at about two o'clock he was awakened by severe precordial pain persisting from thirty minutes to an hour. He sat up in bed grasping his precordium. Occasionally he had a fear of impending death.

On June 12, 1925, a paravertebral alcoholic injection was performed. A very interesting phenomenon occurred while the patient was on the operating table. He suddenly started to groan with pain which was localized to the precordium. Accompanying this excruciating agony he became cyanotic. While in the throes of this anguish, 5 cc. of 1 per cent novocain solution were introduced paravertebrally into the first and second dorsal nerves. Within thirty seconds pain had completely ceased. Five minutes later 5 cc. of an 80 per cent solution of alcohol were introduced into each of the two dorsal nerves. The next day he walked 150 yards as fast as he could, and although he became alarmingly cyanotic and dyspneic, he asserted definitely that he had no pain. Since the treatment, he has been able to walk about comfortably with almost complete absence of precordial pain. He has had no further attacks of nocturnal pain.

Sensory findings June 11, 1925, before the injection.

A. Epicritic sensibilities. (1) A zone of hypesthesia extended over the entire left side of the chest both anteriorly and posteriorly. (2) He had great difficulty in discriminating differences in fine degrees of temperature on the left side, both anteriorly and posteriorly. (3) Cutaneous localization was definitely impaired over the entire left side.

B. Protopathic sensibilities. (1) An area of hyperalgesia extended over the skin segments supplied by the first and second intercostal nerves on the left side. (2) A zone of hyperthermalgesia was observed on the left side over the first and second intercostal spaces. He found no difficulty in discriminating between extremes of temperature over the hyperirritable zones.

*Case Summary.* (1) Because of attacks of angina pectoris, the chest of a patient suffering from thrombotic processes, both in his interbrain as well as in the coronary arteries, was examined by sensory tests, which revealed disturbances in the afferent systems conveying impulses to the thalamus. Nevertheless, a zone of hyperalgesia was found over the skin areas supplied by the first and second intercostal nerves on the left side. (2) Because of signs pointing to a progression of the thrombotic process in his thalamus, it became quite evident that little information would be obtained by comparing the sensory examination of the chest before the injection with that after the injection. (3) No ill effects or complications of any kind following the injections have been observed. (4) He has now been relieved for approximately eight months.

CASE V.—This patient, N. B., a male, aged sixty-five years, suffering from angina pectoris, due to coronary-artery disease, has complained of pain over the heart for a period of two years. The pain was chiefly located over the precordium and radiated down the left upper extremity and was described as constricting in nature and at other times as sticking in type. Often the pain was boring, seeming to penetrate anteroposteriorly. The attacks often occurred two or three times daily. Almost every night about two o'clock he would be awakened by a terrific pain over the precordium, accompanied by a sense of suffocation and a fear of impending death. Venesection was resorted to several times. Morphia relieved him, but amyl nitrite was of little avail. Physical examination showed a greatly enlarged heart with a marked dilatation of the aorta.

A paravertebral injection of alcohol was made into the second, third, fourth and fifth dorsal roots, which relieved him of further attacks, both



during the day as well as during the night. Shortness of breath still persisted upon excretion. Since the injection he has had several attacks of pulmonary edema with absence of pain. Before the treatment these attacks were always accompanied by severe, agonizing pain. Nine weeks later, during which time there was no pain, he suddenly died of pulmonary edema.

Sensory examination before and after injection showed the following:

September 15, 1925, before the injection.

*A. Epicritic sensibilities.* (1) A zone of hyperesthesia to cotton wool was found over the skin supplied by the first to the sixth intercostal nerves on the left side. (2) There was no disturbance noted in his ability to discriminate temperatures ranging between 20 and 38° C. (3) Cutaneous localization was well performed.

*B. Protopathic sensibilities.* (1) A zone of hyperalgesia extended over the skin supplied by the first to the sixth intercostal nerves on the left side. (2) There was noted a greatly increased reaction on the left side to temperature below 20° and above 45° C. He had no difficulty in recognizing these extremes of temperature on the left side.

November 15, 1925. Sixty days after the injection.

*A. Epicritic sensibilities.* (1) There was observed a marked hypesthesia which extended over the skin on the left side supplied by the first to the sixth intercostal nerves, respectively. In fact, he hardly perceived the stroking of the cotton wool over his skin. (2) He was completely unable to discriminate fine differences in temperature, that is, between 20 and 38° C. (3) Cutaneous localization was greatly impaired.

*B. Protopathic sensibilities.* (1) A zone of hypalgesia practically approaching analgesia extended over the skin segments supplied by the first to the sixth intercostal nerves. (2) A marked disturbance in his ability to discriminate between extremes of temperature, that is, below 20° and above 45° C. on the left side was noted. When the affected area was compared with the right side a definite hypothermalgesia was noted to exist over the former.

*Case Summary.* (1) Before the injection of alcohol a zone of hyperirritability existed over the skin dermatomes supplied by the first to the sixth intercostal nerves. Sixty-one days after the injection the conducting function of the intercostal nerves was greatly curtailed. (2) There was no return of pain in spite of the continuance of his attacks of pulmonary edema. On November 19, 1925, he died suddenly during one of these attacks. He was relieved for a period of nine weeks.

**CASE VI.**—Patient, W. H., male, aged seventy-two years, is suffering from angina pectoris due to coronary disease. He was first seen by me December 4, 1925. His attacks of pain began six or seven years before. He described the pain as vise-like and sticking in character. The pain would begin in the precordium and radiate down the left arm. During the last two years, his condition became definitely worse. During the night, he was forced to sit up in bed because of the sudden pain. These nocturnal attacks became so frequent that he would experience this extreme discomfort three and four times nightly. He would remain absolutely quiet and fixed during the attack and felt as though he were about to die. The pain would last from fifteen minutes to an hour. For the past year his attacks would come on consistently, after eating even light meals or after walking a half to one block.

Physical examination showed a moderately enlarged heart with a marked widening of the aorta. A soft systolic murmur was heard at the apex, which was transmitted to the axilla. The heart sounds were of poor quality.

A paravertebral alcoholic injection was made into the first, second, third, fourth and fifth dorsal ganglia. His course twelve weeks after the injection is

as follows: He is able at present to walk twelve blocks without stopping, and there is no pain after this exertion. As was previously observed, the greatest distance he could walk before the injection was a half to one block. His appetite at present is excellent. Before the alcohol injection, the ingestion of even a little milk or cereal would initiate excruciating pain across the chest and down both arms. He would be forced to rise and stand absolutely at rest for as long as one hour before the attack would pass. At present he eats everything, meats, chicken, greasy foods, and so forth. He eats heartily and frequently with no pain. As a result of his increased diet, his general condition has improved. He has gained weight and his muscular tone, as evidenced by his quicker and firmer movements, has increased. The attacks, which occurred three to four times nightly have completely disappeared. Occasionally, during the day he has a sharp, fleeting pain over the precordium. The blood pressure before the injection was systolic 145 mm. and diastolic 85 mm. At present, the systolic pressure is 160 mm. and the diastolic 85 mm.

Sensory examination before and after the injection showed the following:  
December 1, 1925, before the injection.

A. Epicritic sensibilities. (1) A zone of hyperesthesia to cotton wool was found over the dermatomes supplied by the first to the fifth intercostal nerves on the left side. (2) There was observed no disturbance in his ability to differentiate fine gradations of temperature. (3) There was no disturbance in cutaneous localization.

B. Protopathic sensibilities. (1) A zone of analgesia was found to extend posteriorly over the skin segments supplied by the first to the fifth intercostal nerves. (2) A similar zone of diminished sensitiveness to extremes of temperature was noted over the same areas.

*Case Summary.* (1) Before injection a zone of dermatomic irritability extended over the skin segments supplied by the first to the fifth dorsal nerves. Fifty-five days following the injections, signs of marked diminution of nerve conduction were observed. (2) Up to the date of this report, a period of twelve weeks, the patient suffering greatly from angina pectoris has been relieved of his pain. (3) The relief was accompanied by general physical improvement of the patient.

CASE VII.—Patient, G. F., a female, aged sixty years, suffered from angina pectoris secondary to extreme coronary disease. She was referred to us by her son-in-law, a prominent physician in New York, who had observed her constantly for a long time. The following is a letter received from the doctor who gives the history briefly:

"The attacks of pain which Mrs. F. had were paroxysmal in character. The frequency of these attacks was variable, sometimes two and three times a day; toward the end they were almost continuous. The initial attack occurred about three years before, but at that time it was associated with hypertension and usually occurred upon exertion, particularly upon walking in the open.

"Physical examination at the time when you performed the operation was as follows: The heart was considerably enlarged, its action was variable, sometimes perfectly regular, at other times there appeared many extrasystoles. The musculature seemed poor and there were no adventitious sounds. The blood pressure varied between 130 and 140 mm. systolic and between 80 and 90 mm. diastolic. Originally the blood pressure was in excess of 200 mm.

"The condition at the time of exitus I cannot give you in detail. Following the operation, the patient's attacks changed from painful to nonpainful ones and for twelve hours preceding exitus, her breathing was regular,

heart action good, pulse full, rate about 100. The blood pressure was not taken. The exitus was sudden, so that the desired observations were not made. Signs of pulmonary edema appeared in the last moments but death was cardiac in origin."

The condition of this patient before injection was extremely poor. She was in great distress from pain and required constant hypodermic injections of morphin. In fact, her condition was so poor, that the inadvisability of carrying out the therapeutic measure was seriously considered. The distress was so great, however, that the procedure was tried to give her her only chance for relief. For five days following the injection she had no pain. She could eat better and was able to recline flat on her back with only one pillow under her head, whereas before she required three to four pillows. Her color became good, and she was permitted to sit in a chair. On the sixth day, she died suddenly. As observed by her physician, there was no pain during this sudden attack.

A preliminary sensory examination was done before the injection. A zone of hyperirritability was found to extend over the skin supplied by the first to the ninth dorsal nerves on the left side. These nerves were blocked. Each root was injected with 7 cc. of an 85 per cent solution of alcohol. Following the injection, sensory examination showed these roots to be destroyed, as they carried few peripheral sensory impulses.

*Case Summary.* (1) An old woman, suffering from severe cardiac pain due to advanced coronary disease, was injected with alcohol paravertebrally. (2) Her condition was so poor that the inadvisability of injecting was seriously considered. (3) Following the injection she was completely relieved of pain. During this period of freedom from pain she died suddenly.

CASE VIII.—This patient, M. A., male, aged sixty-two years, was first seen by me October 26, 1925. His complaints of pain over the precordium began approximately five years before. The pain was constricting in character and localized over the precordium and down the left arm. These attacks during the past five years were brought on by extreme exertion and were fleeting in character. As time went on, the severity of the pain became markedly aggravated and the frequency increased to as many as two to three attacks daily. He used nitroglycerin constantly. In fact, he dared not move about without having the drug with him. Eight months before the injection, his condition became extremely aggravated. His repeated attacks during the day were severe and agonizing, persisting for ten or fifteen minutes and requiring nitroglycerin and absolute cessation of activities. During the night, he was frequently awakened by these severe attacks. There was with each attack the fear of impending death.

Physical examination showed an extremely enlarged heart and aorta. No adventitious sounds were heard. The heart sounds were faint and distant. His blood pressure was systolic 145 mm. and diastolic 80 mm.

On October 27, 1925, a paravertebral injection of alcohol was done on the left side. Seven cubic centimeters of an 85 per cent solution of alcohol were introduced into the first, second, third, fourth, fifth, sixth, seventh, eighth and ninth dorsal nerves.

The following are the sensory findings observed before and after the injections:

October 26, 1925, before the injection.

A. Epicritic sensibilities. (1) A zone of hyperesthesia to light touch with cotton wool extended over the skin segments supplied by the first to the ninth dorsal nerves, posteriorly and anteriorly. (2) Discriminating powers for temperatures ranging between 20 and 38° C. were intact. (3) Tactile localization was normal.

*B. Protopathic sensibilities.* (1) A zone of hyperalgesia to pin prick extended on the left side of the skin segments supplied by the first to the ninth dorsal nerves. (2) A marked hyperthermalgesia was noted over the above corresponding skin segments. There was observed no abnormality in his ability to differentiate extremes of temperature.

March 1, 1926. One hundred and twenty-five days after injection.

*A. Epicritic sensibilities.* (1) A zone of hypesthesia was observed to extend over the skin areas that previous to injection showed hyperesthesia. In fact, he hardly perceived the stroke of the cotton wool. (2) A marked hypothermesthesia was observed. He found great difficulty in differentiating fine degrees of temperature. (3) Cutaneous localization became greatly impaired.

*B. Protopathic sensibilities.* (1) Instead of the previous hyperalgesia extending over the first to the ninth dermatomes, a marked hypalgesia almost approaching analgesia was observed. (2) His ability to feel extremes of temperature was greatly impaired.

*Case Summary.* (1) Before injection a zone of dermatomic irritability extended from the first to the ninth dorsal nerves on the left side. Sensory examination, one hundred and twenty-five days after the injection showed that the nerve conductivity was greatly reduced. (2) His condition at present is as follows: (a) He requires no nitroglycerin. (b) The attacks of pain although still present are exceedingly mild and fleeting. Before injection they lasted ten to fifteen minutes, or as long as an hour, requiring large doses of nitroglycerin. The pains were so excruciating as to cause extreme anguish and fear of impending death. The pains now are very light and transitory, disappearing in a few seconds. There has been only one attack of pain during the night since the injection. His attacks of pain before injection alarmed his family exceedingly because of the general picture of extreme misery that he presented. Now the family is hardly aware that he has an attack of pain. He has now been comfortable for eighteen weeks.

*Summary.* This paper is presented to correlate our previously observed clinical findings in patients complaining of severe cardiac pain with the information obtained by others through animal experimentation. The clinical observations showed, that subjectively, the pain was relegated to areas of the skin which were supplied by nerves arising between the eighth cervical and seventh thoracic spinal segments (C 8 to D 7). These very same skin areas to which the patients subjectively referred the pain showed them to be hypersensitive to protopathic tests (Head Zones). These findings indicated that the pain impulses were passing through the rami communicantes and ganglia, which were to be found between the eighth cervical and seventh thoracic spinal segments (C 8 to D 7). The indifferent operative results ensuing from procedures upon the cervical sympathetic chain and other nerves in the neck indicated by their failure to ameliorate the pain, that the painful charges were not passing through these structures in their course to the sensorium. A review was made of 41 patients suffering from severe cardiac pain, who were treated by paravertebral block. The injections were confined to those rami communicantes found between the eighth cervical and seventh (C 8 to D 7) spinal segments. The gratifying results obtained seem to quite directly suggest that these rami

communicantes and ganglia are the true conveying pathways of the pain impulses to the spinal cord so as to reach the spinothalamic tracts. The résumé of the animal experimentation supports the clinical observations. This showed clearly that the impulses were passing up through those rami communicantes and ganglia found between the eighth cervical and sixth thoracic. Such nerves as the depressor nerve and the vertebral nerve, rarely observed in humans, were stimulated in animals and failed to incite painful reactions. A perusal of all the data indicates quite clearly, that the future surgical procedures for the relief of cardiac pain must have their attention relegated to the rami communicantes found between the eighth cervical and seventh thoracic spinal segments (C 8 to D 7).

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### CLINICAL AND ROENTGEN RAY FINDINGS IN THE STUDY OF THE HEART AND THE GREAT VESSELS.\*

STUDY OF 100 CASES FROM THE CARDIAC CLINICS OF THE  
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DURING the past thirty years of Roentgen ray investigations, various students of the cardiovascular system have emphasized certain aspects of the Roentgen ray examination of the heart and great vessels. Zinn,<sup>1</sup> in 1898, made a diagnosis of patent ductus

\* Read at the Philadelphia Roentgen Ray Society, October 6, 1927.

arteriosus on the basis of a systolic murmur heard in an area of dullness in the third interspace to the left of the sternum and a marked systolic pulsation seen in the region of the pulmonary artery on fluoroscopic examination. Groedel,<sup>2</sup> in his treatise on the Roentgen ray examination of the heart and the aorta, includes fluoroscopic examinations, but, more particularly, Roentgen ray plates of the characteristic silhouettes of the various cardiovascular lesions. Groedel's studies are made in correlation with electrocardiographic studies and in respiratory phases, and with orthodiagraphic tracings, and include precise measurements of the heart and great vessels. Assmann's<sup>3</sup> work on the heart adds a great deal to studies of the pulmonary area, and, perhaps, more exact data on congenital heart disease from a Roentgen ray standpoint than previous writers. He also ascribes a shadow to the left of the heart as due to syphilitic aortitis. The work of Vaquez and Bordet<sup>4</sup> can best be summed up as an exhaustive study of the heart and the aorta, with orthodiagraphic studies made in well-defined positions, with teleradioscopic, teleradiographic and clinical findings. McPhedran and Weyl<sup>5</sup> have made Roentgen ray studies of the chest during different phases of the cardiac cycle, particularly in diastole of the heart, and also during different phases of respiration with the purpose of defining more clearly lung pathology. The first work by Roentgen ray in the differential etiology of cardiac disease of infectious origin was probably done by Ledbetter, White and Holmes<sup>6</sup> in reference to the causes of aortic regurgitation, the supracardiac shadow due to syphilis being absent in aortic regurgitation due to other causes, notably rheumatic fever. The importance of this finding is evident from the vast difference in the prognosis and therapy in these two forms of cardiac disease.

Abreu,<sup>7</sup> in the radiologic study of the great vessels, uses anatomic preparations in corroborating his Roentgen ray technique in vascular shadows and their differentiation, as well as exact studies of the aorta in well-defined positions. Pendergrass<sup>8</sup> emphasizes Roentgen ray studies in lateral views of the heart with more exact observations on the cardiophrenic area, the normal straight shadow seen in this area being interpreted as a composite shadow of the reflection of the pericardium to the left diaphragm, the inferior vena cava and the posterior phrenopericardial ligaments. This shadow is best seen in the left lateral position with the left side next to the film. Distortion of this shadow is found in adhesive pericarditis and in pericarditis with effusion. In pericarditis with effusion, this work is invaluable when surgical procedures are indicated, more particularly when pericardiocentesis is done posteriorly. Pendergrass further demonstrates the value of lateral Roentgen ray study in determining the site and size of aneurysms of the aorta, in which the distance of the aneurysm from the chest wall must be determined before wiring can be employed as a surgical measure for the relief of cardiovascular disease.

In the present study, we have attempted to study the heart, particularly in phases of respiration, with the purpose of determining the effect of this process on the circulation as seen with Roentgen ray and of throwing more light on the physiology of the cardiovascular and respiratory mechanism. Our object has been also to correlate more definitely Roentgen ray studies with clinical findings in the diagnosis of cardiovascular disease.

All patients are primarily subjected to a fluoroscopic examination. The degree of pulsation, the presence or absence of arrhythmias, changes in the normal cardiac silhouette, dilatation of the aorta, enlargement or marked pulsation of the pulmonary area, presence of aneurysm, ventricular hypertrophy and presence or absence of pericardial adhesions are noted. This examination includes fluoroscopic studies in the anterior-posterior positions, the right anterior oblique position for more exact study of the pulmonary area, lateral positions for study of the mediastinal space and pericardial adhesions, and the right posterior position. The lateral bending positions in the anterior-posterior position also demonstrate the low and fixed position of the apex sometimes seen in adhesive pericarditis. These examinations are made during phases of inspiration and expiration. Left ventricular hypertrophy is estimated in the right posterior position with the patient in varying angles. We have found in a series of normal hearts that the apex of the heart should disappear behind the left border of the spine at approximately 40 degrees or less. If an angle of 45 degrees is necessary to cause such disappearance, we regard hypertrophy as probable and as certainly present in excess of that. Error results unless care is taken that the central ray passes through the cardiac shadow at right angles to the spine.

In addition to fluoroscopic studies, films are made at two meters distance, the target being centered over the spine on a level with the angles of the scapulæ. The patient should be instructed to hold his breath at the end of quiet inspiration. We have made a series of comparative films on normal and obese patients, and on patients with endocardial and congenital heart disease, at the end of deep inspiration, sustained with the glottis closed, and at the end of deep expiration sustained with the glottis closed, and during quiet sustained inspiration. The changes in the cardiac silhouette were somewhat more apparent in those made during deep inspiration, sustained with the glottis closed, but the comparative changes in the silhouette of the cardiac areas were easily visualized in all phases of respiration and in the different types of patients.

From the films, we confirm and correlate our fluoroscopic findings. The transverse diameter of the heart, aorta and the chest are measured. The measurement of the chest is taken from the inner border of the ninth rib, just below the diaphragm in place of the dome of the latter which some prefer as a basal chest measurement.

We arbitrarily consider the heart to be enlarged if the transverse diameter is over 50 per cent of that of the chest.

We find that the normal heart shows, diagrammatically, one curve on the right side, that of the right auricle and right auricular appendage. The left border has four curves: the arc of the aorta, the arc of the pulmonary artery, of the left auricle and that of the left ventricle. In the cardiac silhouette by fluoroscope and film, the curves of the pulmonary artery and the left auricle are not definitely differentiated (Fig. 1a). Indeed, we are of the opinion that when this differentiation is demonstrable, the heart is definitely abnormal. Groedel<sup>2</sup> observes that the character of pulsation of the pulmonary artery and the left auricle, differentiates these two areas. Abreu<sup>7</sup> gives as visible contours, "the right auricle, the superior vena cava, partly covered by the right bronchus; the arch of the aorta which hardly extends beyond the spinal column; the commencement of the descending aorta, the remaining part being invisible because of the pulmonary artery; and the left ventricle."

From the functional behavior of the heart and great vessels during phases of respiration, in the course of fluoroscopic examination, and from the study of the cardiac silhouette on films, we have classified hearts as inspiratory in type or expiratory in type. In quiet respiration, there is little change in the cardiac contour in normal or in diseased hearts, or in those with congenital defects as comparative plates show. In deep inspiration sustained with the glottis closed, there are marked changes in the silhouette of normal hearts<sup>9</sup> and less change in the silhouette of diseased hearts (Fig. 8c, d, e, f). In forced inspiration, the cardiac shadow is better defined, partly due to greater contrast in shadows as a result of increased aëration of the lungs and partly due to the respiratory effect on the circulation and behavior of the heart during respiration. The electrocardiographic tracing taken during phases of respiration: quiet respiration, forced inspiration and forced expiration in each of the usual three leads, show marked respiratory variations in the rate of the heart beat and in the amplitude of the waves in the three leads (Fig. 2) which correspond to changes in the heart silhouette and behavior of the heart during these phases of respiration. Pulsations are apparently more forceful in inspiration as demonstrated by fluoroscopic examination. Murmurs are best heard on deep sustained expiration as the heart is apparently nearer the chest wall, possibly because of some intrinsic circulatory phenomenon.<sup>10</sup> Clinically, we find the disappearance of murmurs on deep sustained inspiration, and the reappearance of murmurs on deep sustained expiration. This is of diagnostic importance in detecting murmurs, particularly in congenital heart disease.

We have found in the obese patient an expiratory type of heart, with usually increased measurements on deep sustained inspiration, and conversely decreased measurements or no change in measure-



ments on deep sustained expiration, in contradistinction to the measurements usually found (Fig. 1*b, c, d, e*). We believe that the heart normally rotates posteriorly on deep inspiration, due to the descent of the diaphragm and the attached pericardial ligaments. In the obese patient with a high diaphragm, we believe that the heart rotates anteriorly on deep inspiration or shows no change of position, remaining transverse. In the normal heart, the ventricular measurements are decreased on deep inspiration and increased on deep expiration. The electrocardiogram of the obese patient usually shows left axis deviation (Fig. 3). There may be hypertrophy of the heart and it may be questioned if this type of heart is normal or at least normal in physiology. The obese patients show dyspnea on exertion and it may be that the anatomic change in the position of the heart and resultant effect on the great vessels due to rotation and torsion is a mechanical factor in causing the dyspnea as well as an explanation for the anatomic change of electrical axis.

The silhouette of the "Schlaffen heart" (Groedel<sup>2</sup>), we think, corresponds to the expiratory type of heart and to the obese type with a high diaphragm (Fig. 1*d, e*). In tracheal obstruction, with increased negative pressure, we believe the heart is inspiratory in type (Pendergrass,<sup>8</sup> Fig. 209). The vertical type of heart seen in tuberculosis (Fig. 5*a*) and emphysema, we consider inspiratory in type. We observe the inspiratory type of heart in mitral stenosis (Fig. 5*b*). We have found, in this series of 100 cases of heart disease, that hearts that are not normal, approach one or the other of the two types of hearts from a Roentgen ray and clinical standpoint. The silhouette of the inspiratory type of heart corresponds to the normal heart during forced inspiration and is vertical in position. The expiratory type of heart corresponds to the normal heart during forced expiration and is transverse in position. These two types of hearts we believe correspond to variations in vital capacity. Campbell<sup>11</sup> observes a decreased vital capacity in mitral stenosis and shallow breathing, which seems to agree with our observations on the inspiratory type of heart. We believe that these two types of hearts correspond also to variations in intrathoracic pressure and to variations in intrathoracic and intraabdominal pressure relations during respiration, and to variations in the capillary circulation in the lungs. Wagoner,<sup>12</sup> in experimental work in animals, found that amounts of fluid aspirated intraabdominally varied with the size of the animal and its type of breathing. Intraabdominal negative pressure increased during inspiration and greater amounts of fluid were aspirated, the deeper and more rapid the breathing. Groedel<sup>13</sup> speaks of the shift of the blood during inspiration and expiration as a protective mechanism, particularly in diseased conditions of the cardiovascular system. Abnormally high or low insertions of the diaphragm, mechanical interference in the heart itself due to valvular lesions, with hypertrophy of the heart and pressure changes in

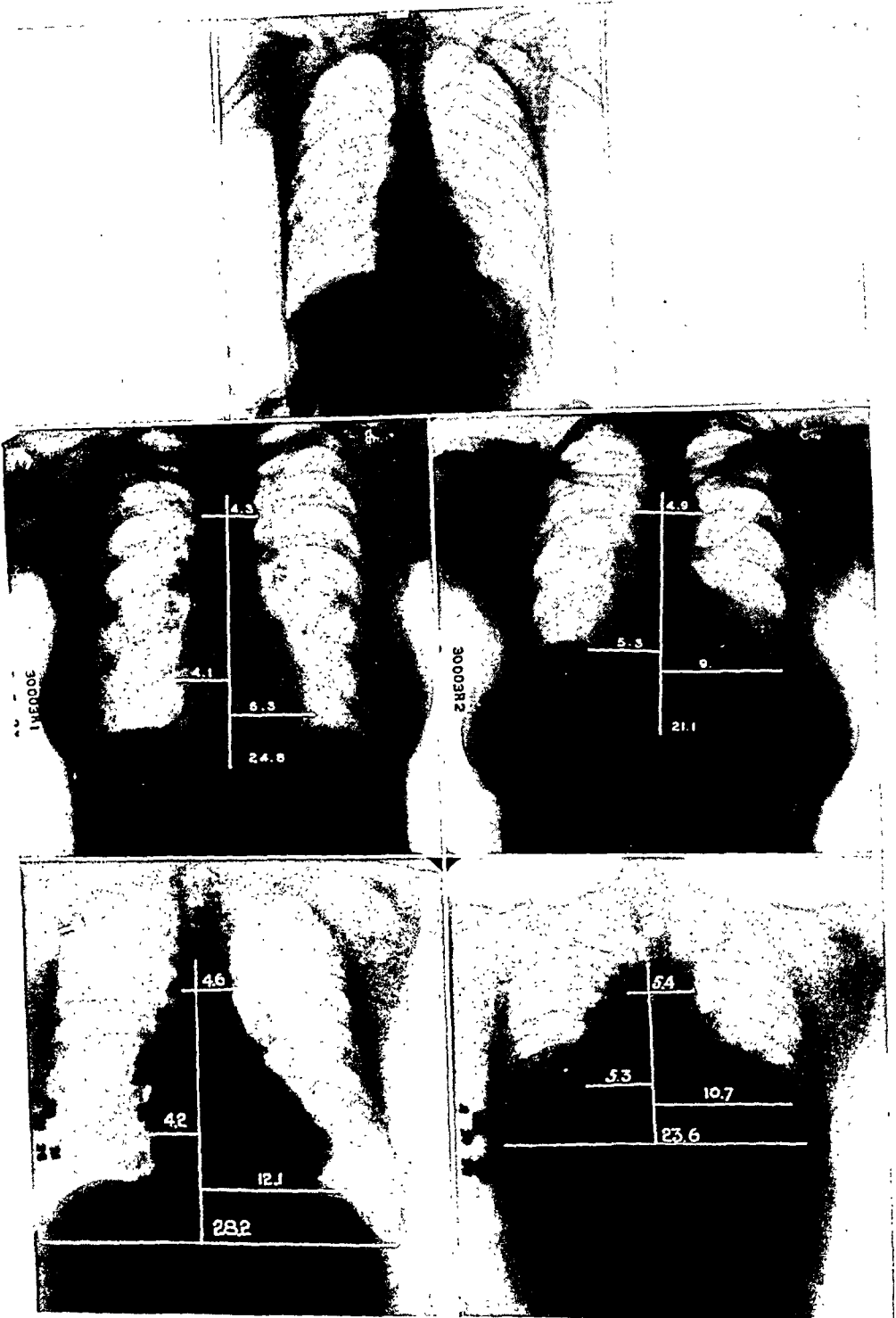


FIG. 1.—A, child, quiet respiration; B, adult, forced inspiration; C, same in forced expiration. Obese type. D, adult, forced inspiration; E, same in forced expiration. Note paradoxical change in measurements due to forward rotation during inspiration.

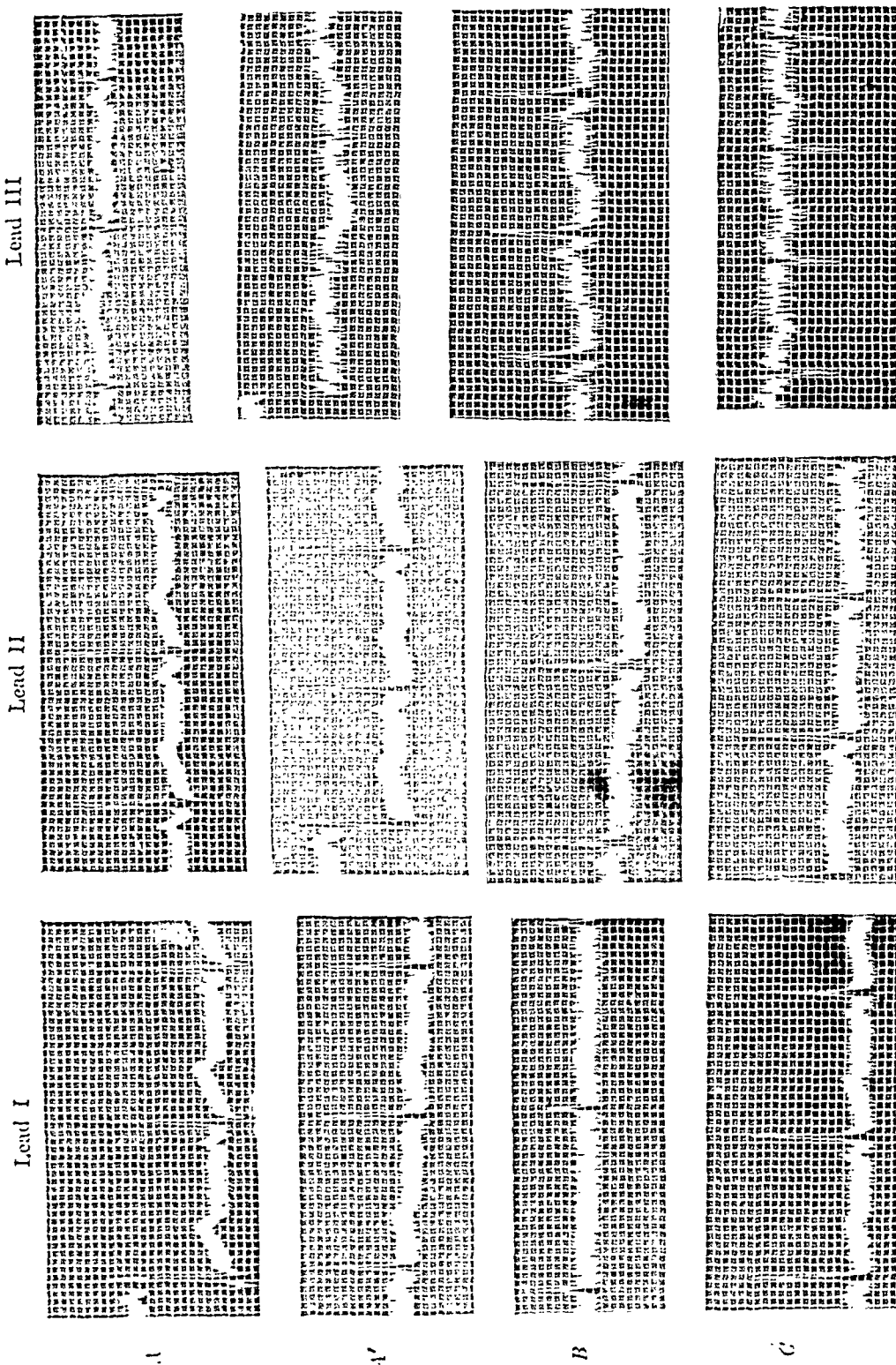


FIG. 2.—Electrocardiographic tracing on normal (Fig. 1 B, C). A, normal tracing in usual manner. Physiologic experiment, Leads I, II, III. A', quiet respiration; B, forced deep inspiration sustained with glottis closed; C, deep expiration, sustained with glottis closed. (Note change in rate and amplitude of waves.)

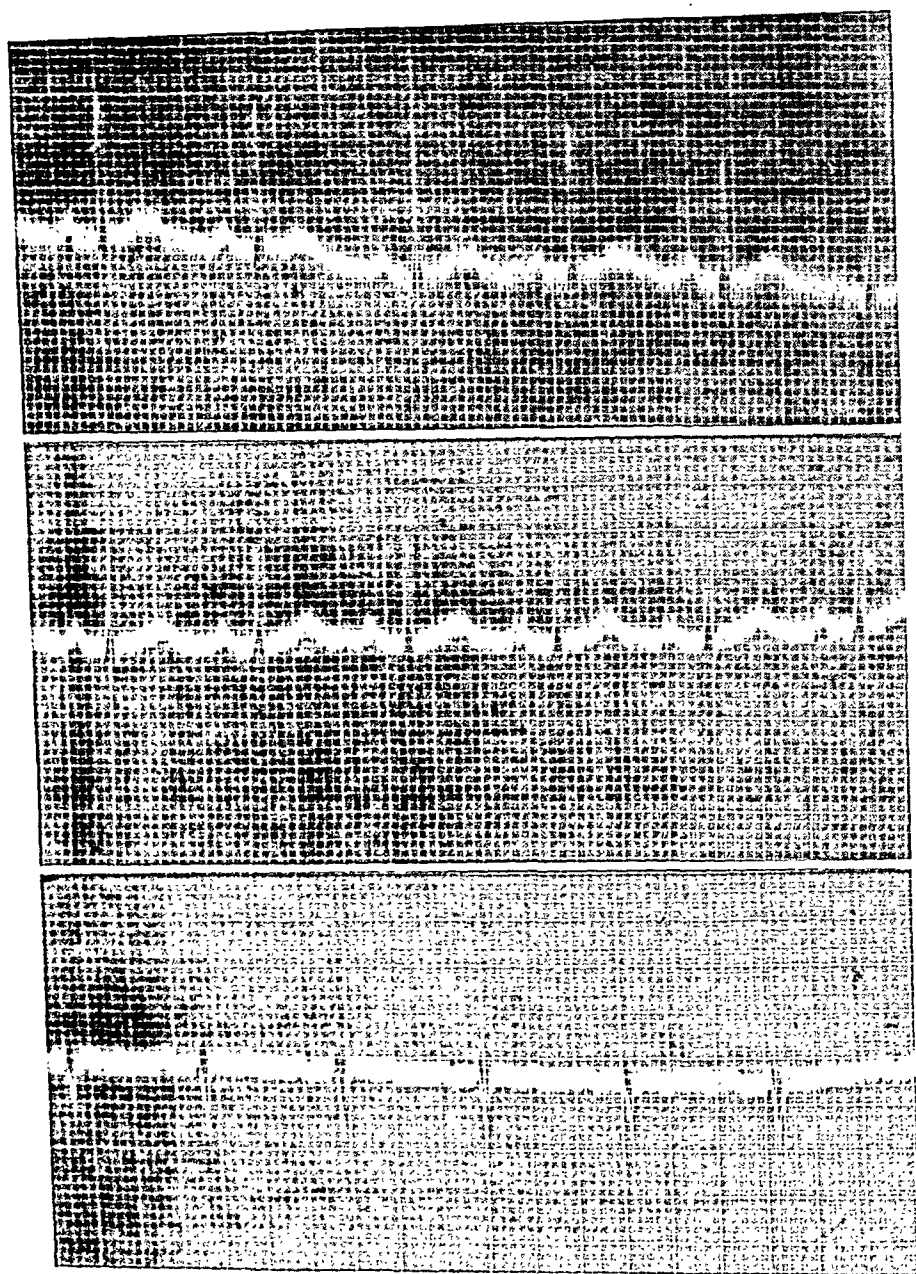


FIG. 3.—Electrocardiogram on obese patient (Fig. 1 D, E) taken during quiet respiration. Note left axis deviation of Q-R-S group.

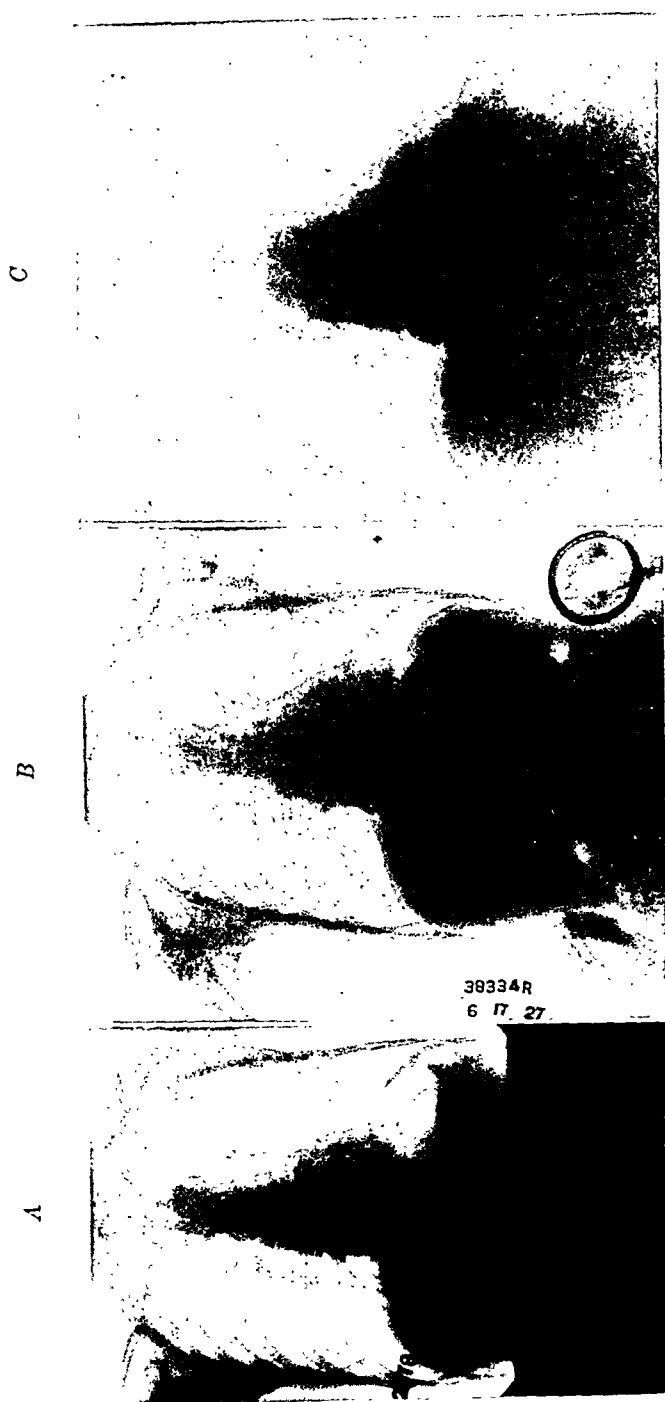


FIG. 4.—Overactive heart. *A*, normal silhouette with bulge of aorta; *B*, note bulge over the pulmonary area; *C*, note bulge of aorta due to hypertension in adult.

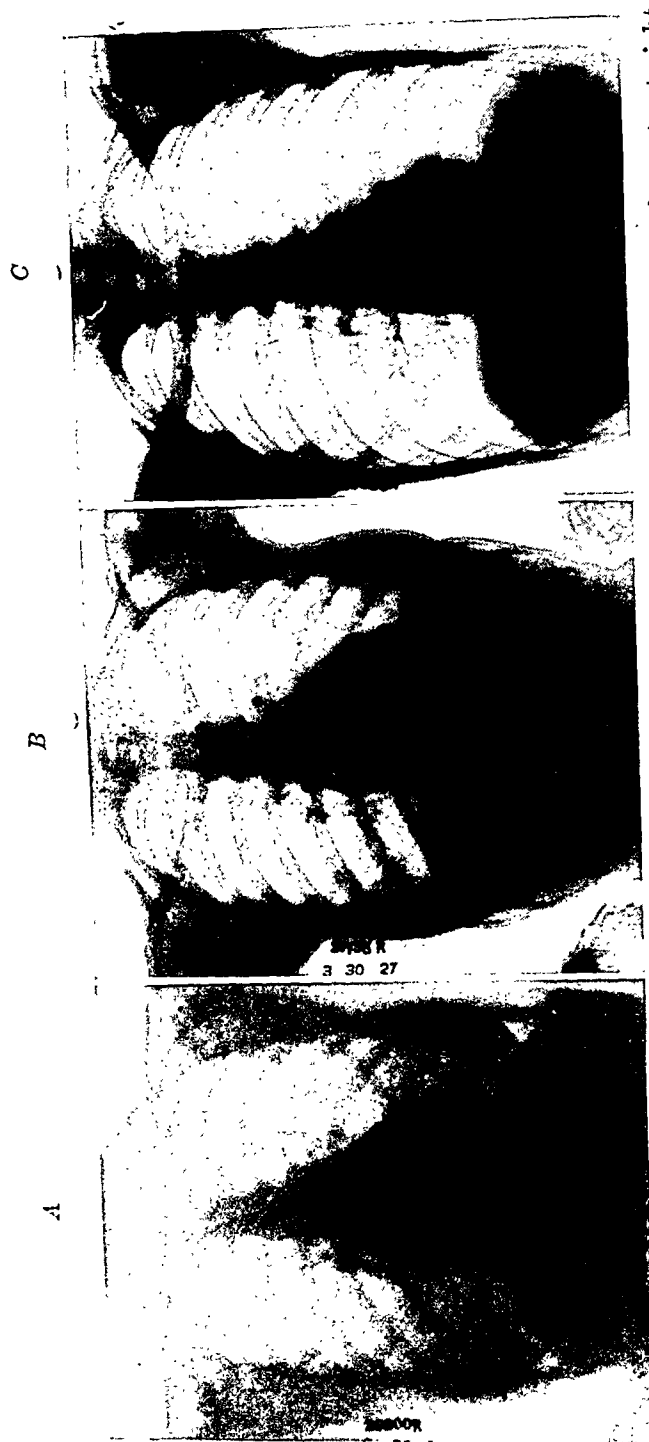


FIG. 5.—A, mitral regurgitation with cardiac silhouette modified by tuberculosis; B, early mitral stenosis—note straight left border due to hypertrophied left auricle (inspiratory type of heart); C, early mitral disease, no change in cardiac silhouette.

*A**B*

FIG. 6.—Mitral regurgitation. *A*, child; *B*, adult.

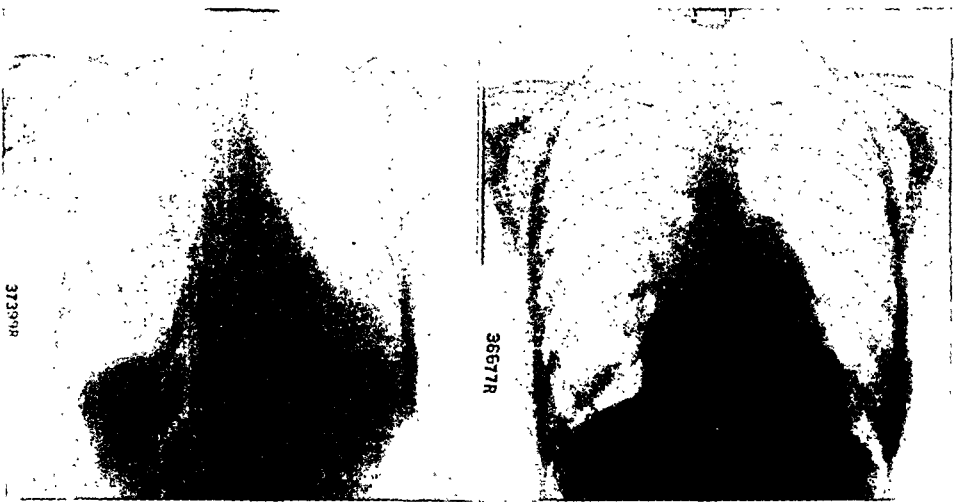
*A**B**C**D*

FIG. 7.—Mitral regurgitation. *A*, with mitral stenosis; *B*, primary mitral stenosis; *C*, with acquired pulmonary stenosis—note bulge over pulmonary arc; *D*, with all valves involved except those of pulmonary artery. (Note hypertrophied right side of the heart due to tricuspid regurgitation).

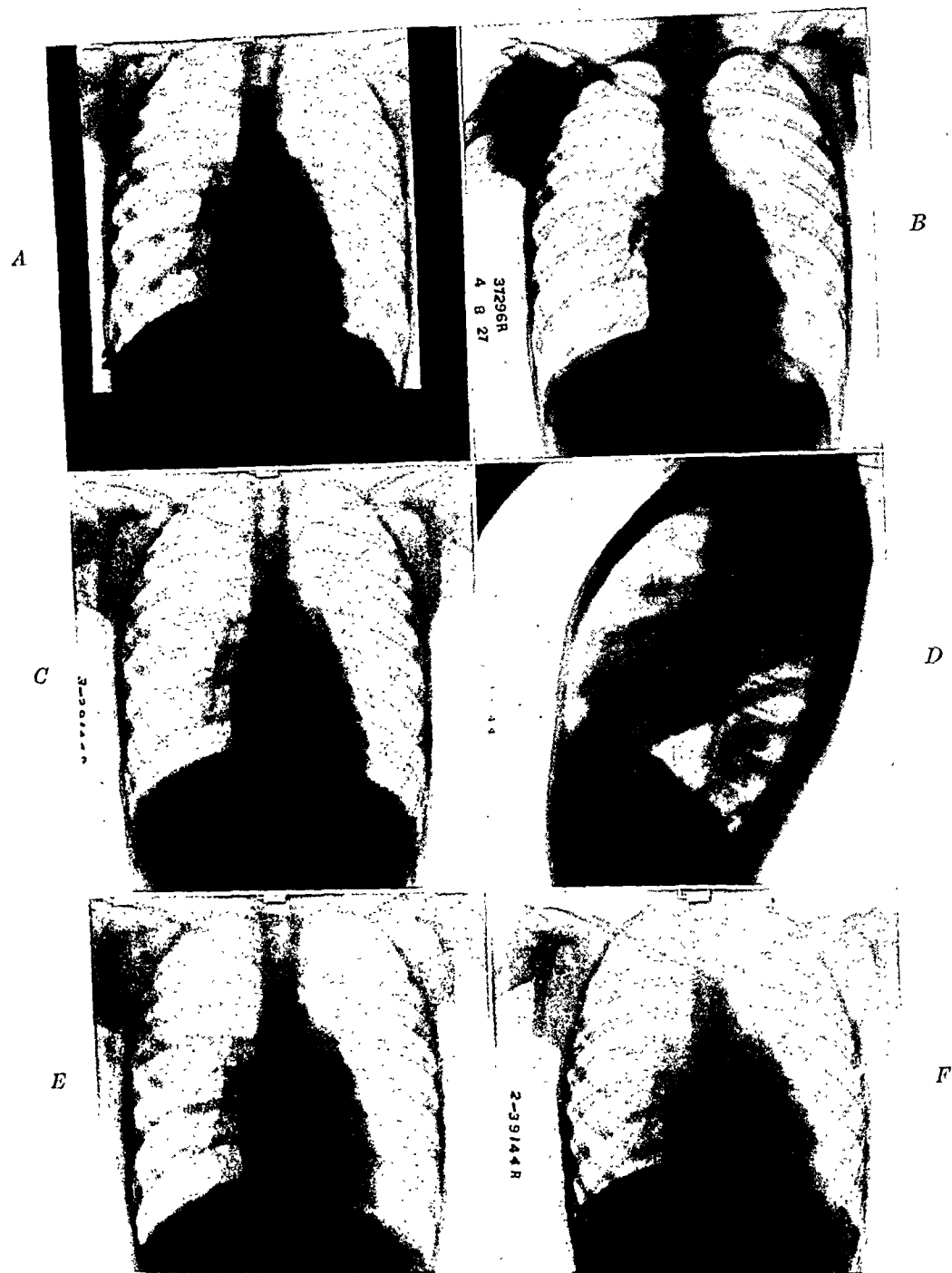


FIG. 8.—Comparative study of mitral stenosis with pulmonary dilatation; patient growing progressively worse. Dilatation of pulmonary artery with diastolic murmur at times, early signs of decompensation with passive congestion. A, May, 1925; B, April, 1927; C, forced inspiration; D, lateral, quiet respiration; E, quiet respiration; F, forced expiration; C, D, E, F, August, 1927. Inspiratory type of heart.



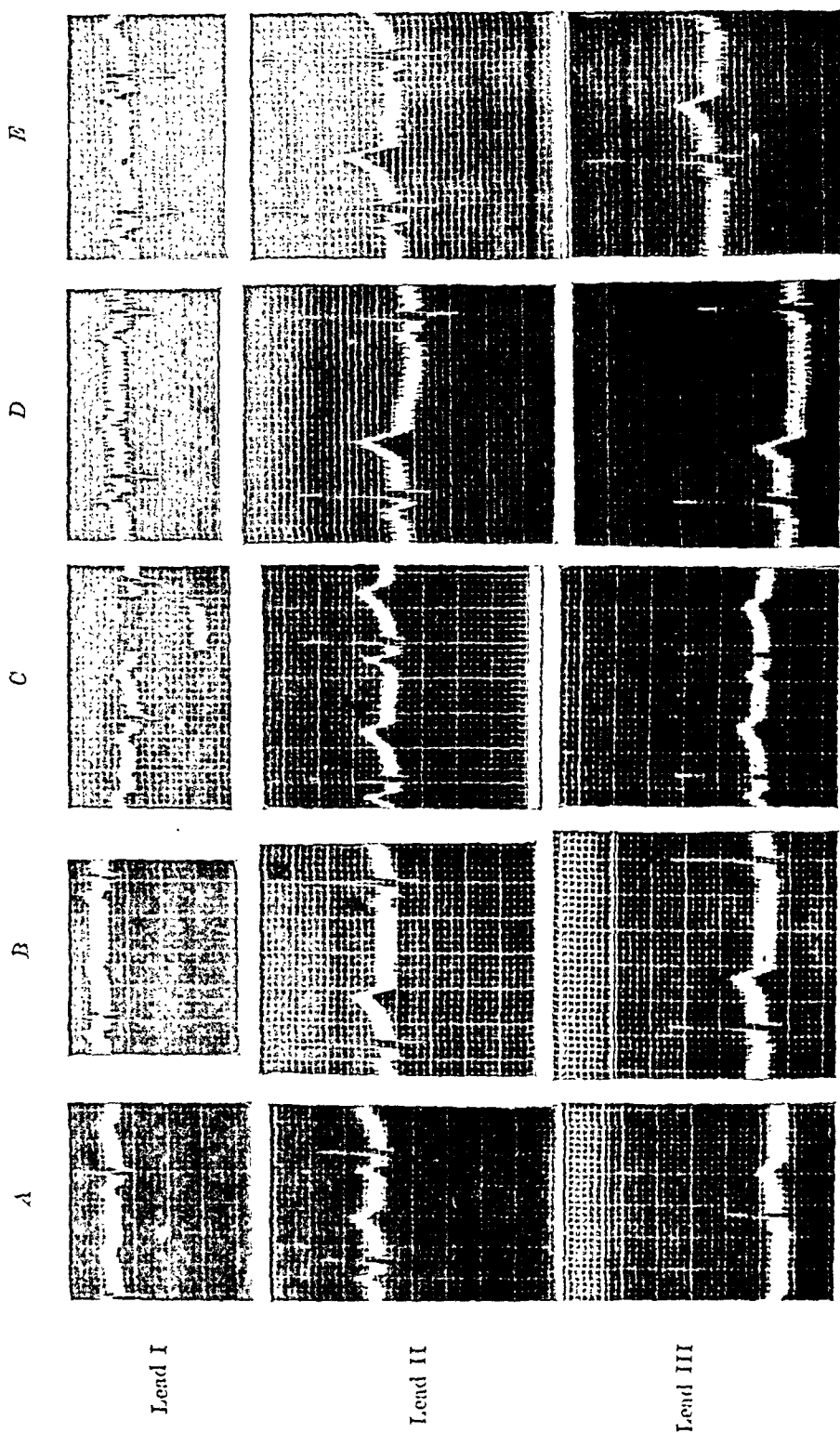


FIG. 9.—Progressive electrocardiographic changes, showing increasing right axis deviation and increasing amplitude of T wave. Patient of Fig. 8. A, November, 1923; B, December, 1923; C, May, 1925; D, April, 1927; E, September, 1927.

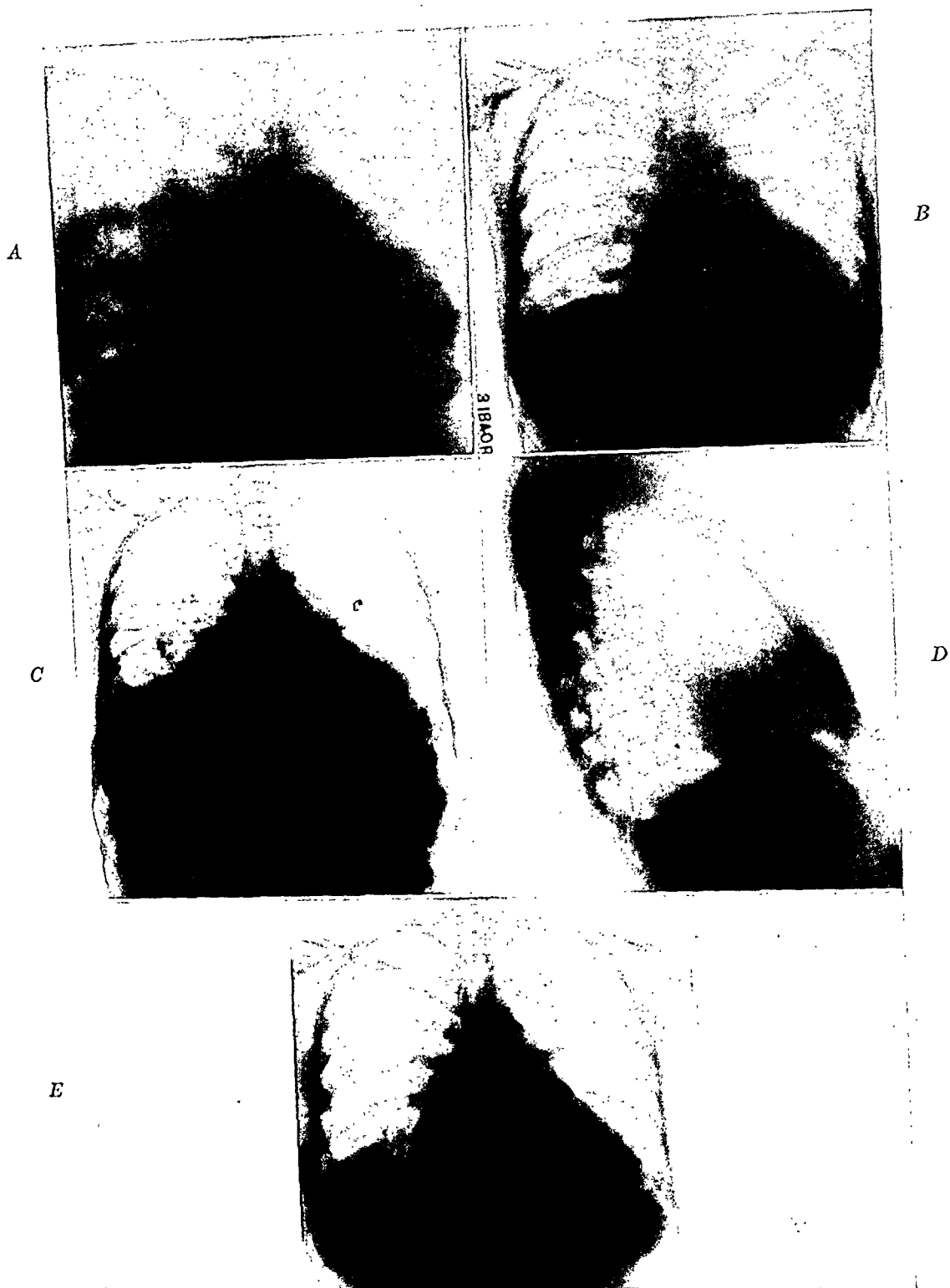


FIG. 10.—Terminal results of endocarditis (mitral regurgitation and stenosis associated with pulmonary and aortic regurgitation, probably also tricuspid regurgitation). *A*, January 25, 1926; *B*, March 19, 1926; *C*, December 3, 1926; *D*, *E*, June 2, 1927.

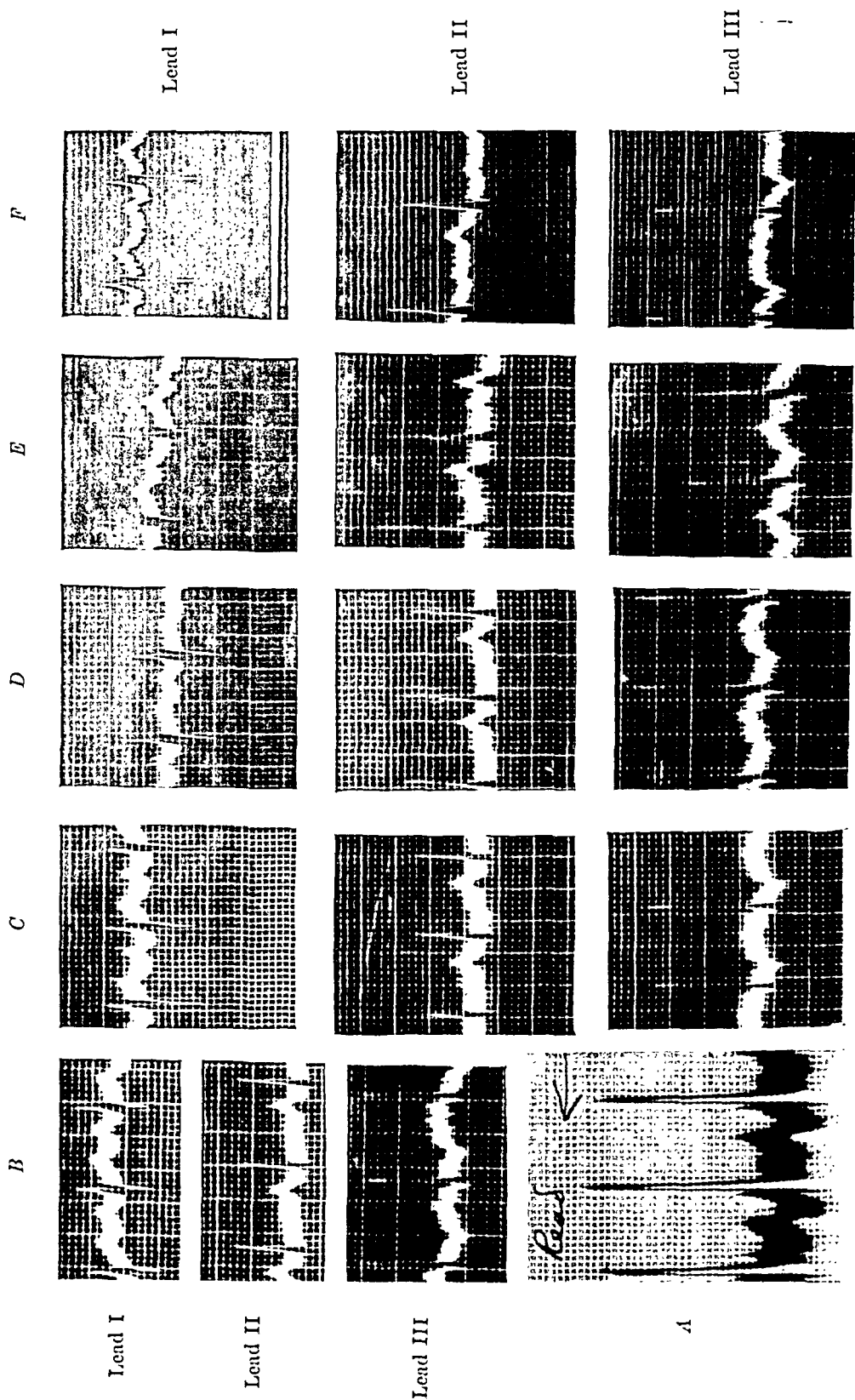


FIG. 11.—A, radial pulse tracing, January 15, 1926, collapsing type, seen in aortic regurgitation. (Aortic diastolic murmur in presence of pulmonary diastolic murmur.) Electrocardiographic tracings showing changes in axis deviation and slight changes in P and T waves. B, January 15, 1926; C, February 5, 1926; D, March 8, 1926; E, March 19, 1926, P-R interval slightly prolonged; F, December 3, 1926.

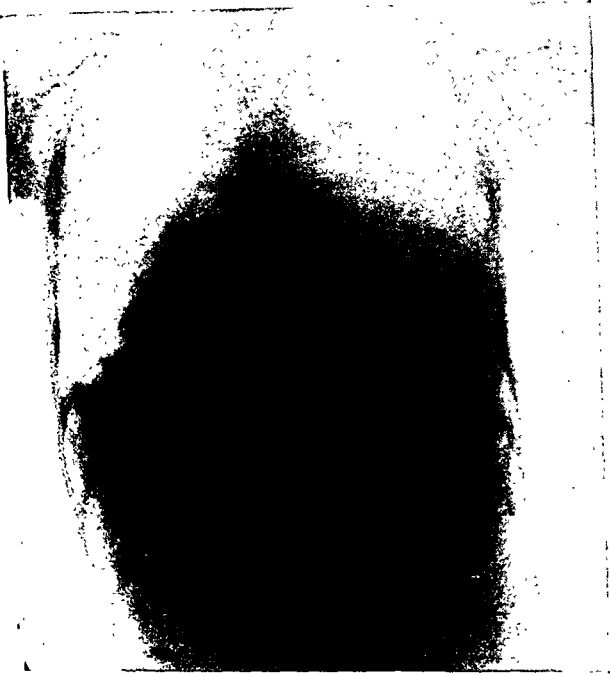


FIG. 12.—Pericarditis with effusion.

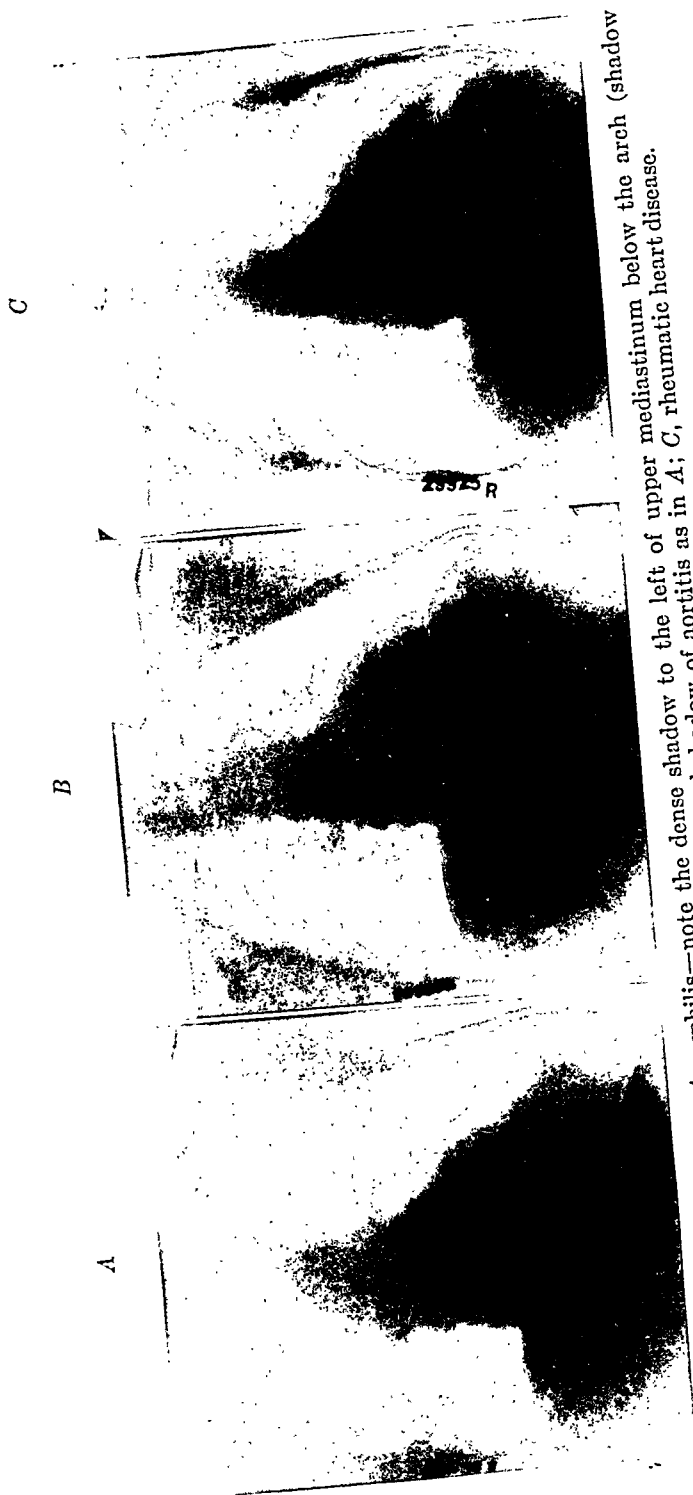


FIG. 13.—Aortic regurgitation. A, syphilis—note the dense shadow to the left of upper mediastinum below the arch (shadow of associated aortitis); B, syphilis, no associated shadow of aortitis as in A; C, rheumatic heart disease.

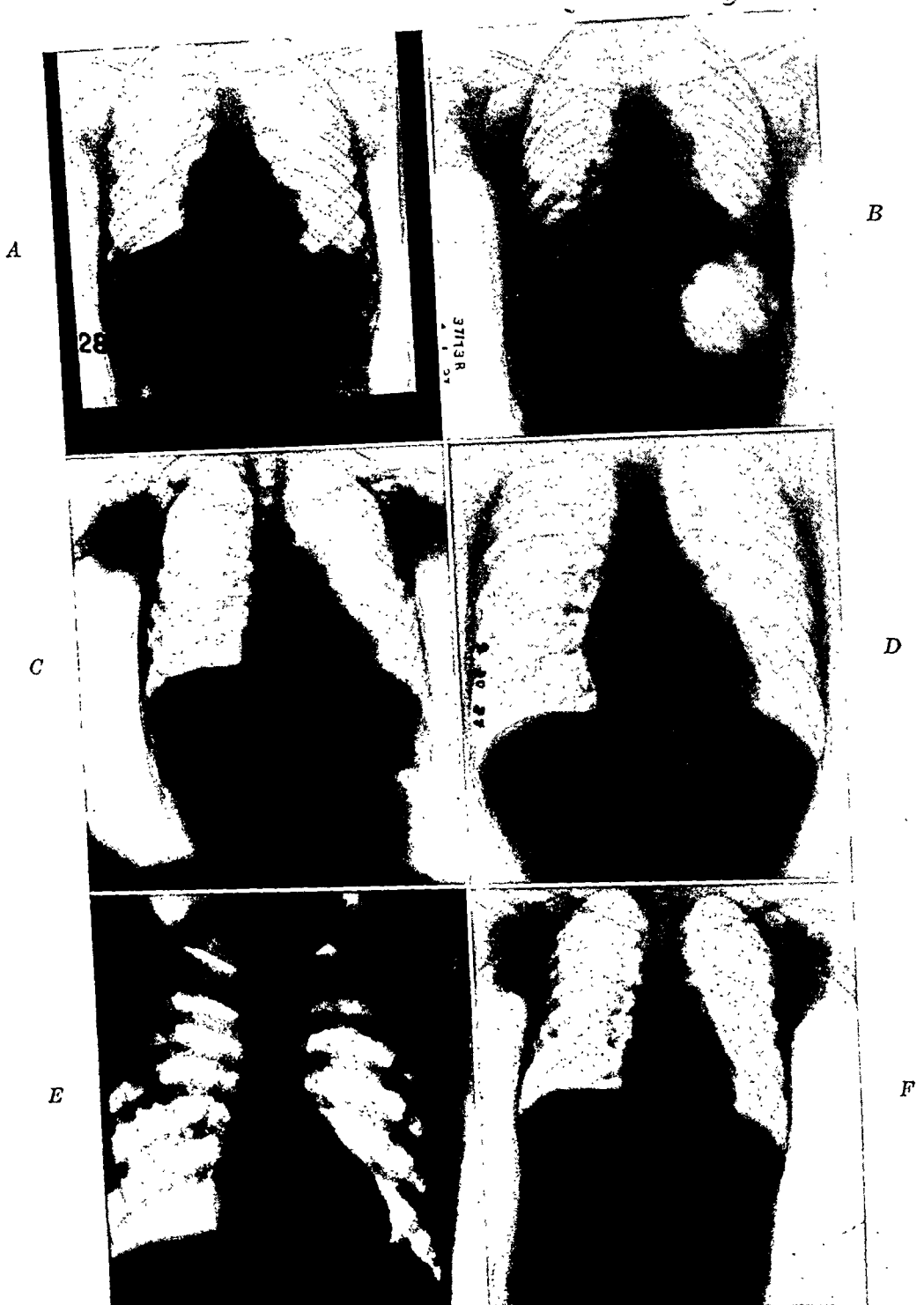
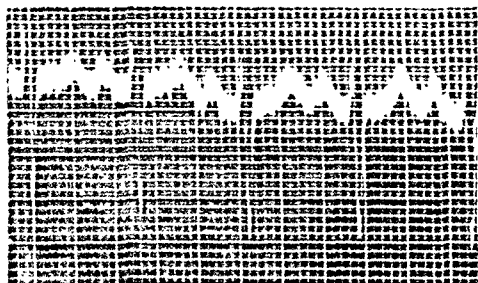


FIG. 14.—Congenital heart disease. A, clinically, patent ductus arteriosus, confirmed by fluoroscopic examination; normal silhouette; B, patent ductus (note bulging over the pulmonary arc); C, patent ductus with septal defect (two distinct murmurs heard); D, congenital pulmonary stenosis; no bulging over the pulmonary arc; E, congenital pulmonary stenosis; autopsy examination showed presence also of septal defect; note more globular type of heart than D; F, mitral regurgitation with question of congenital heart (patent ductus) or acquired pulmonary stenosis. Silhouette would militate against diagnosis of patent ductus.

A



B

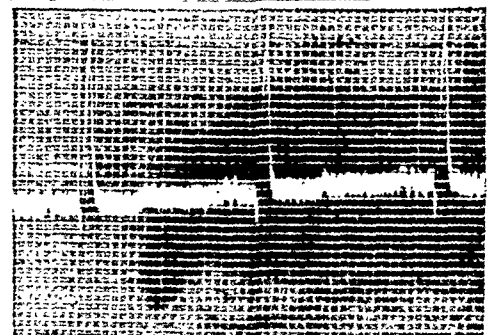
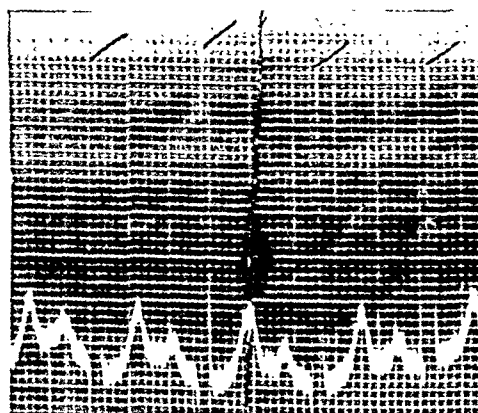
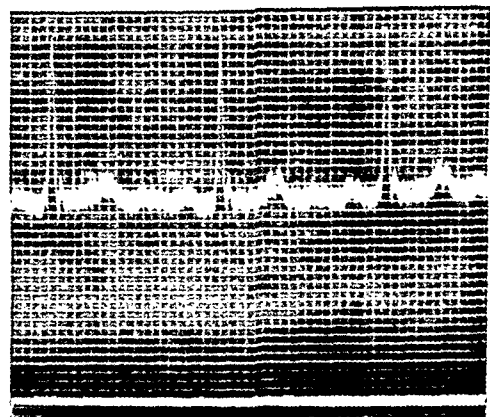
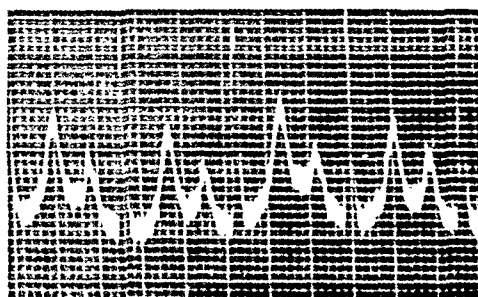
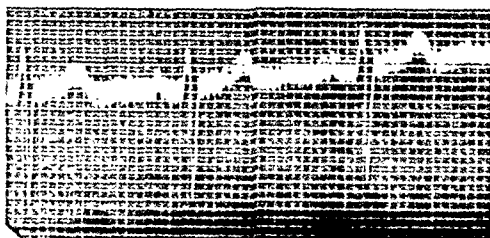


FIG. 15.—Electrocardiograms in pulmonary stenosis, congenital. A, marked right axis deviation and marked increase in amplitude in *T* wave. Corresponds to patient 14-D (pulmonary stenosis); B, marked right axis deviation; corresponds to patient 14-E (pulmonary stenosis with septal defect).

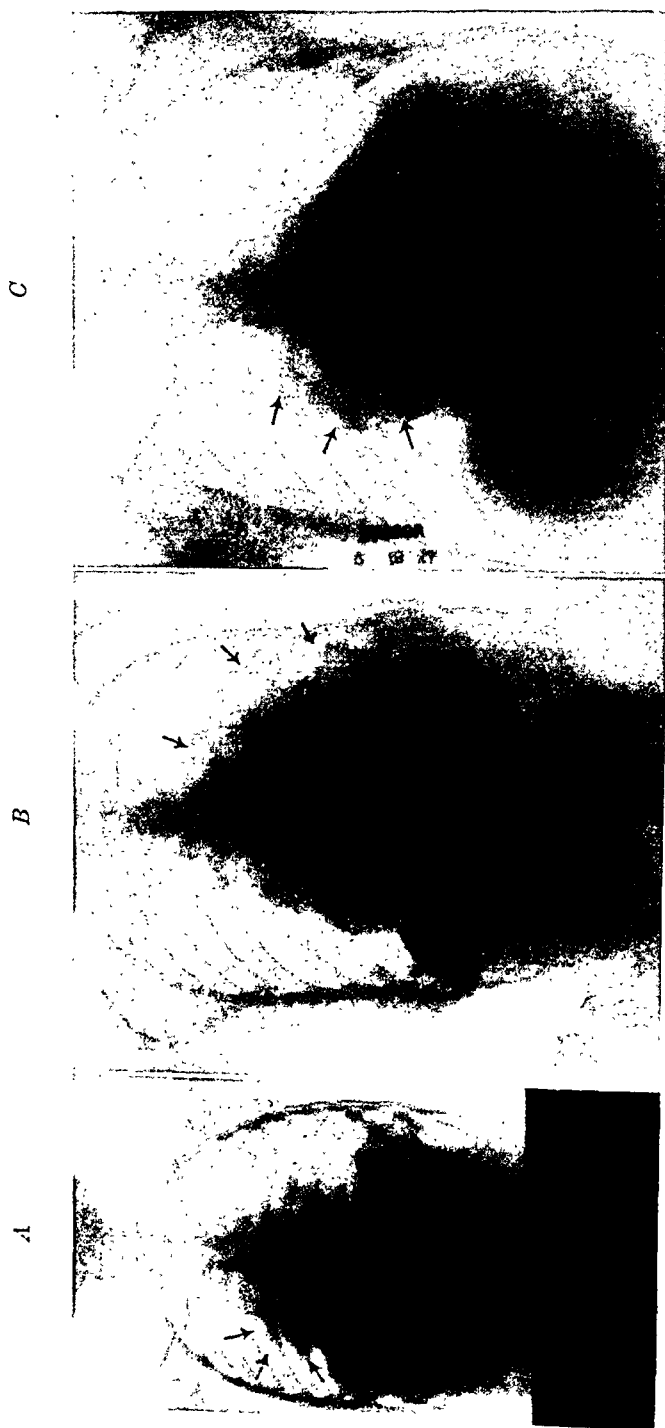


FIG. 16.—Cardiac aneurysms. *A*, congenital septal defect between aorta and base of right ventricle, aneurysm also of right ventricle; *B*, aneurysm of left ventricle, congenital in origin; *C*, acquired aneurysm of right auricle.



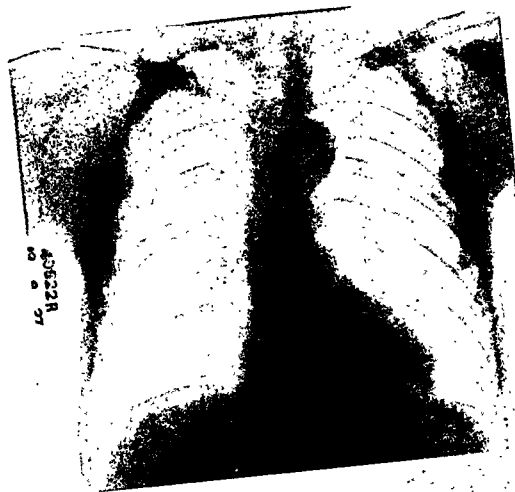


FIG. 17.—*A*, arterial sclerosis, chronic lead poisoning; no endocardial disease; note upward tilting of the shadow of aortic arch; *B*, enormous saccular aneurysm of horizontal arch of aorta; note atheromatous plaques throughout the course of aorta from its origin to the termination of its thoracic division; *C*, lateral view of *B*.

the great vessels, changes in the hydrogen-ion activity of the blood and carbon dioxide content controlling respiration, decrease in the capillary field due to disease of the lungs and decreased bloodflow, tracheal obstruction, atonicity of the heart muscle or faulty habits of breathing may also be factors involved. We believe, however, that from a Roentgen ray and clinical standpoint this functional classification of hearts as inspiratory or expiratory in type is explanatory and is not an arbitrary deduction from the study of the cardiac silhouette by fluoroscope and film, but that it is based on definite normal and pathologic physiology underlying the mechanism of respiration and fluid distribution in the body and that further study along these lines may demonstrate principles of value in surgical procedures in the chest, particularly in the "rationale" of removal of fluid by surgical intervention. Such study may demonstrate indications general measures along the therapeutic lines of the physical factors involved, particularly in relation to intraabdominal and intrathoracic pressures and the muscular tension of the abdominal walls.

In a series of children or young adults, we have observed types of hearts which we arbitrarily have termed over active hearts. In one type, we find marked pulsation of the aorta on fluoroscopic examination and some bulge of the aorta arch on films (Fig. 4a). In the other type, there is marked bulge of the pulmonary artery on fluoroscopic examination and bulge of the pulmonary area by film (Fig. 4b). Clinically, the overactive heart with an abrupt first sound and an accentuated pulmonic second sound simulates at times mitral stenosis. Bulging of the pulmonary artery in mitral stenosis usually occurs in advanced stages of rheumatic heart disease. It seems that the type showing increased aortic pressure, as demonstrated by pulsation and contour of the aorta by film, is part of hypertension in children, and the type related to the pulmonary or venous circulation, part of an increased pressure tension in the venous side of the circulation, which seems to occur in the child without demonstrable cardiac disease as a basis. Some of our blood-pressure determinations in children show arterial hypertension according to the standards set by Faber.<sup>14</sup> Such overactive hearts, we feel, should be studied for evidence of disease or disturbance of function elsewhere. We have found left and right axis deviation respectively, in the electrocardiographic records in some of these overactive hearts without demonstrable cardiac disease.

We will now discuss our findings under the individual abnormal cardiovascular conditions.

**Hypertension.** In hypertension in the adult, we do not believe there is a characteristic silhouette by Roentgen ray (Fig. 4c). Hypertension can be suspected by the marked pulsation seen over the entire cardiac and aortic field. Chronic hypertension shows

left ventricular hypertrophy and left axis deviation by electrocardiographic study. Simple hypertension or "early essential hypertension" with normal arterial walls gives more than normal pulsation with some dilatation of the aorta, which shows by film as a symmetrical accentuation of the normal aortic silhouette. Later, the silhouette is modified by sclerosis or other fibrotic changes.

**Mitral Disease.** In definite early mitral disease, the Roentgen ray findings may be normal (Fig. 5c). Progressive mitral disease shows hypertrophy of the left ventricle (Fig. 6a, b). However, since hypertrophy of the left ventricle is the only change noted in the cardiac silhouette in cases of uncomplicated mitral regurgitation, and since other etiologic factors can be responsible for such hypertrophy, this form of mitral disease cannot be diagnosed from the Roentgen ray outline alone. With well-marked mitral regurgitation, some stenosis of the mitral valve is also present. This is probably the cause of the more or less straight border from the base of the pulmonary artery to the apex of the heart, due to definite auricular hypertrophy (Fig. 7a). Where stenosis is the predominating lesion, there is definite bulging of the left auricle in addition to ventricular hypertrophy (Fig. 7b). The cardiac silhouette of mitral stenosis and regurgitation with definite enlargement over the pulmonary area must be differentiated from that of other conditions associated with increased pressure in the pulmonary artery with dilatation of the artery, as in patent ductus arteriosus, from conditions of increased pressure in the right heart with hypertrophy of the conus of the right ventricle,<sup>15</sup> and from conditions of pulmonary stenosis, congenital or acquired with right ventricular hypertrophy (Fig. 7c). Here, again clinical evidence is necessary to diagnose the pathologic condition and to interpret the Roentgen ray findings.

When we see, in children, during and after acute rheumatic fever, more than normal pulsation of the pulmonary artery and hear a systolic murmur at the pulmonary area, we are forced to the feeling that the pulmonary valves and artery are frequently involved in endocarditis and that acquired pulmonary stenosis may develop much the same as mitral stenosis does and frequently accompanies it. Occasionally, in well-marked mitral stenosis, when the disease is actively progressing, there is a blowing diastolic murmur over the pulmonary artery which may be inconstant due to dilatation of the pulmonary artery,<sup>16</sup> and fluoroscopically, there is more than usual pulsation of the artery and bulge of the pulmonary area by film. This type of mitral stenosis is most distressing (Fig. 8a, b, c, d, e) and indicates marked and long cardiovascular strain.<sup>17</sup> The case from which this illustration was obtained also showed progressive right-axis deviation in the electrocardiogram and increased voltage of the T wave (Fig. 9a, b, c, d, e). We have observed the same type of murmur, "the Graham Steel murmur,"<sup>18</sup> in an adult with actively progressing mitral disease of the regurgitant type, with the presence

also of an aortic diastolic murmur (Fig. 10*a, b, c, d, e*). This patient showed a collapsing type of pulse and electrocardiographic changes (Fig. 11*a, b, c, d, e, f*). One of our cases had clinical signs of tricuspid regurgitation with mitral stenosis and regurgitation (Fig. 7*d*), bulging of the pulmonary area in the film and an accentuated pulmonic second sound heard clinically. We detected no clinical signs of pulmonary regurgitation.

**Pericarditis.** The differential diagnosis of pericarditis<sup>19</sup> with effusion must be made from mediastinal tumors, pleural effusion and right- and left-sided hypertrophy in mitral and tricuspid regurgitation (Fig. 12). The clinical history of acute pericarditis is definite and the clinical signs are evident. With effusion, on fluoroscopic examination, we note a more or less globular contour of the heart, absence of differential pulsations of the various arcs of the cardiac silhouette and a waving characteristic movement of the heart shadow. Lateral views may show a convex outline of the pericardial reflection to the dome of the diaphragm instead of a concave one as is normally seen (Pendergrass).

In chronic adhesive pericarditis, the lack of mobility of the apex is visualized on fluoroscopic examination and the heart does not show the normal shadow separating from the shadow of the diaphragm on inspiration. Films occasionally show deformity of the pleuro-pericardial diaphragmatic shadows and it is probably because of these adhesions that many pleuropericardial friction sounds are heard clinically. The fluoroscopic study helps to explain the low and fixed position of the apex seen particularly in mitral stenosis accompanied by pericarditis.

**Aortic Insufficiency.** In aortic regurgitation due to syphilis, there is usually considerable deflection of the aorta as a whole with each systole (Fig. 13*a, b*). This left-sided swing of the aorta as a whole is the result of a high pulse pressure, systolic thrust and a marked diastolic recoil due to rapid changes in blood pressure or to actual blood regurgitation, within walls more or less damaged by disease and hyperfunction. We find commonly an associated aortitis which is readily diagnosed by films. We note a typical shadow to the left of the upper mediastinum below the horizontal arch, which extends from the shadow of the arch to the base of the left auricle (Fig. 13*a*). This shadow we have observed only in cases of aortitis and it is probably due to aortitis with dilatation of the descending aorta. Often this shadow seems to merge with that of the lower border of the arch and it obscures the pulmonary artery and the auricle on fluoroscopic examination and film and it is sometimes difficult to exclude an aneurysm (Fig. 13*a*). Differentiation is always possible however on fluoroscopic examination since in aortitis if the patient is turned from the anterior-posterior position into the right oblique position, the shadow cast by the dilated descending aorta can be made to disappear so that the horizontal arch with the left border of

the heart can be clearly traced. If aneurysm is present the silhouette of the arch is obliterated. This shadow of aortitis is additional evidence of the value of Roentgen ray in differentiating the causes of aortic regurgitation, as we never observe the shadow of aortitis in cases of uncomplicated rheumatic origin (Fig. 13c).

**Congenital Heart Lesions.** We do not believe there is a characteristic silhouette by Roentgen ray for any one type of congenital heart disease.<sup>20</sup> In patent ductus arteriosus, congenital heart disease of the noncyanotic type or type "cyanosis tardive,"<sup>21</sup> a characteristic and marked pulsation in the region of the pulmonary artery seen on fluoroscopic examination, in the presence of a palpable thrill and a marked systolic of a machinery murmur in a corresponding area of dullness in the third interspace to the left of the sternum, is presumptive evidence of this congenital anomaly. One of our cases of patent ductus shows a normal silhouette by Roentgen ray, a normal electrocardiogram, and a marked pulsation over the pulmonary area on fluoroscopic examination. There was a marked systolic murmur (heart sounds record gave the pitch of the murmur as 260 vibrations per second), a palpable thrill, no cyanosis and no dyspnea, and the first and second heart sounds were present and normal (Fig. 14a). We usually find marked bulging over the pulmonary area in patent ductus (Fig. 14b), due to a left to right shunt of the blood stream. This case had a marked systolic murmur, a palpable thrill to the left of the sternum in the third interspace, no cyanosis nor dyspnea. There was, on fluoroscopic examination, marked pulsation of the pulmonary artery. In cases of patent ductus in conjunction with a septal defect, we usually find marked bulging over the pulmonary area, probably due to blood-pressure changes in the right heart because of a left to right shunt of the blood stream due to the septal defect and to increased bloodflow through the patent ductus due to both of these factors. This case had two murmurs of different pitch and origin, one due to the ductus, which was transmitted upward to the left clavicle, and the other due to the septal defect, which was most marked over the sternum and was transmitted equally in this area (Fig. 14c).

In the presence of a prolonged systolic murmur, thrill in the third interspace to the left of the sternum, history of cyanosis from birth, oxygen unsaturation,<sup>23</sup> high red cell count, right axis deviation in the electrocardiogram,<sup>24</sup> and an absence of other murmurs, we have made a diagnosis of pulmonary stenosis, congenital in origin (Fig. 14d). This case had, in addition to right axis deviation in the electrocardiogram, unusually high voltage of the *T* wave. The second case (Fig. 14e) which we diagnosed as pulmonary stenosis, congenital in origin, proved on autopsy, to have also a septal defect, which probably accounts for the more or less globular type of heart and for the marked difference in the two electrocardiographic records in the two cases (Fig. 15a, b).

We have not found the marked bulging over the pulmonary area in congenital pulmonary stenosis, particularly when complicated by a septal defect. It may be that the gradual development of the circulatory mechanism in pulmonary stenosis congenital in origin, modifies the hypertrophy of the ventricle and adapts it to the added strain due to stenosis of the artery and interference with the circulation. We do find marked bulging over the pulmonary area in acquired pulmonary stenosis (Fig. 7c) and, at times in patent ductus. One of our cases (Fig. 14f) suggested acquired pulmonary stenosis or patent ductus. There was evidence of mitral endocarditis, left axis deviation in the electrocardiographic record and a history of rheumatic infection. The fluoroscopic examination suggested patent ductus by the marked pulsation seen over the pulmonary area. We felt, however, that the evidence made acquired pulmonary stenosis the correct diagnosis. Only the most careful cross checking of Roentgen ray and clinical findings is of value.

**Aneurysm.** The study of cardiac aneurysm antedates study of Roentgen ray by seventy years or more. The older writers give stress and strain, in the presence of weak muscle walls, as a causative factor. Morris<sup>25</sup> and others have shown that coronary artery disease and occlusion are paramount in the causation of aneurysms of the heart. Stress and strain were factors in 2 of the 3 cases of our series. Without fluoroscopic examination, the clinical findings in these cases of aneurysm of the heart could not have been interpreted. In the first case of our series, congenital heart disease was diagnosed from the clinical signs of a systolic murmur heard over the aortic area and midsternum, transmitted to both subclavian arteries, not heard in the carotids, a palpable thrill over the aortic area, presence of first and second sounds at the apex and to right of the sternum in the fourth interspace. There was, what seemed to be a palpable apex beat to the right and left of the sternum. There was cyanosis and dyspnea on exertion and a history of pertussis of severe type. Roentgen ray film showed a bulge to the right side of the heart, extending beyond the limits of the border of the right auricle. Fluoroscopic examination showed the pulsation to be synchronous with that of the left ventricle. Diagnosis was made of septal defect between the aorta and the base of the right ventricle and aneurysm of the right ventricle. (Fig. 16a)

The second of our cases of aneurysm of the heart presented the clinical signs of a systolic murmur over the pulmonary artery and a thrill characteristic of pulmonary stenosis. There was no cyanosis. Fluoroscopic examination showed a circumscribed shadow to the left of the upper area of the heart which had some pulsation not as marked as is usually seen in aneurysm of the heart or aorta. It was rather evident clinically that a mass pressing from behind on the pulmonary artery could give the signs present of pulmonary stenosis. A roentgen diagnosis was made of aneurysm or neoplasm (Fig. 16b). Autopsy (38608) showed aneurysm of the left ventricle,

congenital in origin, clot formation with possible pressure on the pulmonary artery.

Diagnosis of acquired aneurysm of the right auricle was made in the third case of this series, from the fluoroscopic study of the pulsation of a mass to the right of the heart. This man gave a history of severe cough with expectoration for two years. It was evident by fluoroscope that the time of the pulsation of the mass preceded systole of the ventricle. The fluoroscopic and film study showed the circumscribed shadow to be situated anteriorly, superimposed on the upper portion of the right auricle. With enlargement of the heart, time of pulsation of the mass and a history of strain, a diagnosis was made of aneurysm of the right auricle, acquired in type. This man has auricular fibrillation, mitral regurgitation and a history of purpura hemorrhagica. (Fig. 16c)

Aneurysms of the aorta or other vessels are less difficult in clinical diagnosis. Increased supracardiac dullness, relative blood pressure changes in arms, and in arms and legs, bruits and murmurs over the course of bloodvessels, pulsating masses in the course of arteries, history of syphilis and differential pulsations under fluoroscopic study usually make the diagnosis evident (Fig. 17b, c).

**Arterial Sclerosis.** By fluoroscopic and Roentgen ray film examination, we suspect the existence of arterial sclerosis by an upward tilting of the silhouette of the horizontal arch of the aorta, the mechanism of which has been suggested in connection with hypertension (Fig. 17a). The width of the normal aorta is measured by lines parallel with the long axis of the body of the sixth dorsal vertebra. In arterial sclerosis, the arch of the aorta is displaced upward and inward, due to the tortuosity, dilatation and rotation of the aorta caused by an upward thrust exerted by the blood stream on sclerotic walls which lack normal resiliency. The apparent diameter is therefore altered from a horizontal to an oblique line, which makes an angle of approximately 45 degrees with the transverse line paralleling the long axis of the sixth dorsal vertebra. By clinical examination, we, at times, detect atheroma of vessel walls by the murmurs or bruits heard over the vessels. Roentgen ray at times demonstrates atheromatous walls, which may be clearly and definitely visualized (Fig. 17b, c). The electrocardiogram gives evidence at times of fibrotic changes in the heart muscle or conduction system. The presence of sclerotic changes in the eye grounds is additional evidence of cardiovascular sclerosis, and with hypertension, helps to correlate the clinical and Roentgen ray findings in the diagnosis of arterial sclerosis.

**Summary.** One hundred cases of congenital and acquired heart disease have been studied by clinical, electrocardiographic, clinicopathologic and Roentgen ray laboratory methods. We have accepted as normal hearts those without clinical signs or symptoms of disease, and which by Roentgen ray show no hypertrophy, have normal respiratory movements, no unusual pulsations of the

various cardiac areas, particularly of the aortic and pulmonary areas, and which show no axis deviation, arrhythmias nor changes in the conduction system by electrocardiographic examination.

The heart in the obese (5 cases), while normal from clinical examination, usually showed increased measurements on deep inspiration, which we believe is due to an anterior rotation of the heart. The electrocardiogram showed left axis deviation in those showing anterior rotation. All five cases of obesity had dyspnea on exertion. A possible explanation of the dyspnea may be an anatomic one due to anterior rotation or lack of normal rotation with torsion and mechanical pressure on the great vessels and mechanical interference with the circulation. We believe the obese heart is abnormal in physiology, even if not the seat of pathologic changes in structure.

In children and young adults (7 cases), we have found a type of heart without clinical evidence of disease which we have called over-active. Two of the 7 cases showed hypertension and increased pulsation of the aorta by fluoroscopic examination and bulge of the aorta by film. Five of the cases showed marked pulsation of the pulmonary artery and bulge of the pulmonary area by film. One case showed left axis deviation in the electrocardiogram and one case right axis deviation. We feel that such hearts should be studied for evidence of disease elsewhere.

Hypertension in the adult (12 cases) showed marked pulsation of the whole cardiac field, particularly of the aorta. The silhouette of the aorta varied from the symmetrical bulge due to high sustained pulse pressure and dilatation of normal arterial walls to the type modified by arterial sclerosis in which the arch has an upward tilt.

In rheumatic heart disease primarily involving the mitral valve (43 cases), 7 were diagnosed as mitral stenosis with the "inspiratory type" of heart; 21 as mitral regurgitation with some stenosis of the mitral valve and 12 as mitral regurgitation with definite stenosis evident by clinical signs. Three cases were questionable for endocardial disease. Marked pulsation over the left auricle and an inspiratory type of heart were interpreted as evidence of stenosis by Roentgen ray examination. One of the mitral cases had pericarditis with effusion.

In aortic regurgitation of rheumatic etiology (5 cases) one showed endocarditis also of the mitral valve, a *Streptococcus viridans* infection with ulceration through the aortic to the mitral. This case showed a marked acidosis at times (pH 7.22 to 7.28) edema of the subcutaneous tissues and pain, particularly aortic in origin. In aortic regurgitation of syphilitic origin (10 cases) 4 cases showed the shadow of aortitis. The silhouette of the arch showed definite swing of the aorta to the left due to a high pulse pressure unsustained in the presence of weak or diseased arterial walls. Both the shadow of aortitis and the definite swing of the aorta to the left were absent in aortic regurgitation due to rheumatic infection.

In congenital heart disease (8 cases) we found no silhouette



characteristic of any one type of this kind of heart disease. The origin and transmission of murmurs, differential blood pressures, the presence or absence of cyanosis, hypertrophy of the various areas of the heart and the history were cross-checked by electrocardiographic evidence of axis deviation and voltage of the *T*-wave and Roentgen ray study of the pulmonary area. Septal defects give a more or less globular-shaped heart and in the two cases of undoubted pulmonary stenosis, one of which had a septal defect, electrocardiographic records show contrasting features which need further explanation.

Three cases of aneurysms of the heart were studied: one of the right ventricle with a septal defect between the aorta and the base of the right ventricle, and one of the left ventricle, both congenital in origin. These cases gave evidence of congenital defects by murmurs, heart sounds and by Roentgen ray examination. Pulsations of the abnormal masses were timed by fluoroscopic examination and the masses demonstrated by film. The aneurysm of the right auricle, the third of this series, gave no clinical evidence by murmurs.

Aneurysms of the aorta (4 cases) were diagnosed clinically and confirmed by fluoroscope and film. One case died in uremia and autopsy showed the whole heart and aneurysm bound to the surrounding tissues by adhesions in a process of repair. It could never have ruptured.

Arterial sclerosis (3 cases) showed by Roentgen ray a type of heart characterized by an upward tilting of the horizontal arch of the aorta and an oblique diameter of the arch. At times, sclerosis was evident by calcification of the vessel walls. The electrocardiogram is of value in the diagnosis of fibrotic changes in the cardiovascular system and the eye grounds always showed evidence of arterial changes.

In this small series of cases, sex does not seem to be of any importance. Age is an interesting factor in the overactive type of heart in childhood and early adolescence. We have included in our study a case of a woman one hundred years of age whose clinical and laboratory tests were normal. The peripheral capillary circulation showed marked changes due to senility and the patient had a marked sensitivity to temperature changes, particularly to cold. The height and weight ratio were important only in the definitely obese, all of whom gave clinical symptoms. Two of the 43 rheumatic heart cases had positive Wassermann tests and 2 of the 10 hypertension cases also not showing valvular lesions or aortitis. Tachycardia was a factor in the overactive hearts and 12 of the 43 cases of rheumatic heart disease had heart rates over 100. Four of the 100 cases showed definite renal involvement with high diastolic pressures, albumin in the urine and high specific gravity. Anemia was a factor in 3 of the 7 cases of overactive hearts and in 5 of the rheumatic hearts. Forty-two of the 43 cases of rheumatic heart disease gave a history of rheumatic infection: 21 of acute rheumatic fever, 15 of tonsillitis and 16 of focal infection. Thirty-four of these

43 cases of rheumatic heart disease had respiratory infections as measles, pneumonia, bronchitis or pertussis. Seventy-four of the 100 cases studied had a history of the above respiratory infections which seems probably the most important clinical result of this study of cardiac or cardiovascular disease. Three of the hypertension cases had had typhoid fever. Fourteen of the 100 cases had normal electrocardiograms and all but the 2 normal cases included, had respiratory symptoms. Fifty-eight of the entire series showed definite eye-ground changes.

**Conclusions.** We believe that Roentgen ray study helps to demonstrate the functional efficiency of the heart in respiration, the degree of pulsation and relative changes in the various areas of the heart and vessel walls, and that the classification of hearts that are not normal as inspiratory in type or expiratory in type is explanatory and a functional classification of value, based on physiologic study of normal and abnormal hearts.

The heart in the obese is abnormal in physiology, even if not the seat of pathological changes in structure.

The overactive heart is an entity demonstrated by Roentgen ray and confirmed by clinical examination.

Roentgen ray is of value in the diagnosis of hypertension and of mitral disease and in the clinical differentiation of functional from organic heart disease.

We feel that the study of the pulmonary area is worth while in the decision between functional and organic heart disease; that it explains the physical signs as to murmurs, dilatation, and palpable thrills at the pulmonary area; that some of these signs may be due to hypertrophy of the conus of the right ventricle or dilatation or stenosis of the pulmonary artery; that such study is valuable in the diagnosis of pulmonary stenosis and regurgitation and in the clinical differentiation of diseases of the pulmonary and aortic valves where a diastolic murmur is heard at the base of the heart, particularly where the lesion of mitral regurgitation and stenosis is present; that patent ductus cannot be adequately diagnosed without fluoroscopic study; and that all murmurs at the pulmonary area need explanation in terms of definite pathology or disturbance of function.

As is well known, Roentgen ray furnishes additional evidence of pericarditis with effusion and of adhesive pericarditis. The fluoroscopic examination shows the fixed and low position of the apex, particularly in cases of mitral stenosis.

We have nothing new to add to the previous work in the differentiation of the causes of aortic regurgitation, except the possible value of the additional shadow of aortitis of the descending aorta as evidence of aortic regurgitation of syphilitic rather than of rheumatic origin.

Aneurysms are best demonstrated by fluoroscopic examination and the differentiation from other thoracic masses is only possible at times by this method.

Roentgen ray demonstrates arterial sclerosis by a characteristic silhouette of the heart and great vessels, and by the presence at times of atheroma and calcification of vessel walls.

We believe that the rôle of respiratory infections in heart disease is the most important clinical deduction from the present study.

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# THE EFFECT OF AMYTAL ANESTHESIA UPON THE UTERUS AND ITS USE IN OBSTETRICS.

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THE claims which have been brought forth for the therapeutic superiority of each of many derivatives of barbituric acid since the original synthesis of barbital by Fischer and Dilthey<sup>1</sup> may well be doubted.<sup>2</sup> One of these derivatives, "amytal" (iso-amyl-ethyl-barbituric acid) was synthesized in 1923 by Shonle and Moment.<sup>3</sup> From the time of its physiologic introduction by Page<sup>4</sup> amytal has become increasingly popular as a safe and effective anesthetic for animal experimentation. It is thought to possess several negative characteristics, if not virtues, as an anesthetic. When administered to dogs, it does not affect the blood-sugar level,<sup>4, 5, 7</sup> blood concentration,<sup>6</sup> metabolic rate,<sup>7, 8</sup> or blood pH and CO<sub>2</sub> combining power.<sup>9</sup> The most discouraging feature in the use of this compound has been a variability in the solubility and anesthetic potency of the product. This factor in itself was sufficient justification for the exclusion of amytal from "New and Nonofficial Remedies." Furthermore, nothing is known concerning the fate of this substance in the organism. In spite of such significant objections, amytal has been "tried out" on man with apparent impunity.<sup>10, 11</sup> Two years ago, apparently for the first time in this country, one of us had the opportunity to employ amytal anesthesia in human subjects. In this work, the administration of the anesthetic *per rectum* was found very effective.<sup>12</sup>

The peculiar state of hypnosis, resembling "anergic apathy" and the prolonged stupor, characteristically present in dogs given small doses, suggested the possibility that this anesthetic might prove of value in obstetrics. With this aim in view, during the past year the writers have collected data which they feel merit a preliminary report at this time.

**Experimental.** Kymographic records of the contractions of the uteri of virgin guinea pigs were made. In some cases the uteri were studied *in situ* in animals anesthetized with large doses of amytal. In other cases one cornu of the uterus was removed from the animal and studied in a constant temperature bath (Dale) to which high concentrations of amytal were added. In all instances, the rhythmic contractions were maintained under the anesthetic. The response of the uteri to the oxytocic principle of the pituitary (Parke, Davis & Co.) was not disturbed after amytal anesthesia.

Albino rats, weighing about 200 gm., have been found very suitable for the biologic assay or standardization of the amytal preparations. With two preparations of good anesthetic potency, the average dose and time relationships were as shown in the accompanying table:

Mgm. amytal per kilo body weight.	25	50	75	100	150	200
Time in minutes for onset of complete anesthesia . .	Incomplete	4-4½	3	2-2½	1½	1½

The amytal was injected intraperitoneally and the speed of onset of anesthesia in this species was noteworthy. In comparison with dogs, recovery from nonfatal doses was also relatively rapid in rats. About 30 per cent of the rats receiving 150 mg. per kilo body weight and about 60 per cent of those given 200 mg. per kilo died. In rats, therefore, the ratio of the anesthetic dose (50 mg. per kilo) to the fatal dose was somewhat less than 1 to 3. Other preparations of amytal have been assayed by this procedure and found appreciably less potent anesthetically and more toxic than the above. The writers, therefore, consider the "standardization" of the preparations to be administered to patients of prime importance.

Amytal has been used for anesthesia in 33 obstetrical patients. The dosage in the first 30 cases was 25 mg. per kilo of "assayed" preparations given by rectum. In the last 3 cases, the dosage has been 30 mg. per kilo. The advantages of the rectal administration of the drug are threefold: (1) The patient receives the drug believing she is being given an "enema." This permits of nearly a perfect anoci technique. (2) The patient goes to sleep slowly, complete relaxation occurring in from thirty to forty-five minutes. (3) No precautions need be taken in regard to colloidal material in the solution since this presumably makes no difference in the intestinal tract, but is a matter of serious importance in intravenous injection.

**Results.** In 13 cases the result was excellent. By this we mean complete anesthesia throughout the period of delivery. The patients were quiet, apparently in deep sleep, but uterine contractions continued. In 10 cases, the results were classified as good. These patients moaned or moved somewhat during uterine con-

tractions, but between pains were quiet and relaxed. In 7, the results were fair. The patients were quiet, on the whole, between pains, but were noisy and unmanageable during pains. All patients in this group were restrained. Two patients were grouped under poor results. In both of these the uterine contractions disappeared while the patients were under anesthesia and did not begin again until complete recovery from the effect of the amytal. It should be remembered that the disappearance of labor pains after they have begun is not unusual in unanesthetized patients so that the cessation of uterine contractions may not have been due to the amytal.

In the majority of patients, no change took place in the systolic or diastolic blood pressure throughout the period of anesthesia. A drop of over 10 mm. of mercury was taken as definite evidence of an alteration in the blood pressure. This occurred in 5 patients. The maximum drop was 50 mm. When the pressure is high from fright or excitement prior to the administration of amytal, it tends to drop to a normal level as the patient goes to sleep.

The temperature showed very little if any variation and the drop in temperature noted in many animals during amytal narcosis was not observed in these human subjects.

The pulse rate of the patient remained stationary in about one-half of the cases and was raised in the other half. The maximum rise was 30 per minute and this occurred during the period when the head came down on the pelvic floor. The fetal heart rate was unaltered in every patient under anesthesia.

The respiratory rate was rarely affected. In 4 cases it was increased, but in no instance did we observe the very slow respirations which frequently occur after the intraperitoneal administration of the drug to the dog.

The force of the uterine contractions was diminished in 2 patients who subsequently delivered while under anesthesia and completely ceased in 2 patients who recovered from the effect of the drug and were subsequently delivered.

Outlet forceps or high forceps were used or version practised in 17 cases. In 4 of these supplemental anesthesia was used because the patients were apparently in pain although they did not remember having had pain when they finally recovered from the anesthesia.

Two babies were slightly asphyxiated. Both of these were in difficult deliveries. In the remainder the babies cried lustily when born. They were not narcotised nor did they show any other effect of the drug.

The period of sleep from inception to completion of anesthesia varied. In 18 of the cases where careful records were kept, 1 patient was completely awake in six hours, 6 recovered within twelve hours, 5 in eighteen hours, and 6 in twenty-four hours.

**Mortality.** There was one baby born dead in this series. This occurred twenty-seven hours after the administration of the amytal

and at a time when the patient was completely recovered from the effect of the drug. The baby's fetal heart rate was 128 throughout the period of anesthesia. Six hours after recovery from the drug and after a prolonged labor, high forceps were applied. The child was dead when delivered. Though the cause of death has not been definitely ascertained, this has been classified as an amytal death. The mothers all recovered.

The most striking phenomenon was the amnesia which was characteristic of these cases. Not one of the patients who slept remembered the delivery. Even the refractive individuals went to sleep after the birth of the child and upon awakening were loath to believe that the child had been born.

The dose of amytal used in these cases is one-half the anesthetic dose for the dog and rat. With the use of 30 to 35 mg. per kilo of body weight, we believe that even better results may be expected. The writers are particularly anxious, however, to leave the impression that it would be unwise and even dangerous to employ preparations of amytal on patients, unless these preparations have been tested as to potency and toxicity.

**Summary and Conclusions.** Iso-amyl-ethyl barbituric acid (amytal) was found to have no effect upon the rhythmic contractions of the virgin guinea pig's uterus either *in vitro* or *in vivo*. Furthermore, the uterus of animals anesthetized with this drug responded to the oxytocic principle of the pituitary.

A method for the standardization of the amytal solutions has been introduced. The importance of such biologic assay has been pointed out.

The drug has been found to produce effective anesthesia in a large proportion of obstetrical cases. In all of them its administration resulted in a condition of amnesia, so that, after delivery and recovery from the drug, the patient had no recollection of the period of labor.

Very little, if any, effect was noted on the maternal pulse, temperature, or respiration. The blood pressure dropped in 5 of the 33 cases more than 10 mm. of mercury, but was well maintained in the remainder.

The babies at the time of delivery showed little, if any, effect of the drug.

A new method for the administration of the drug was presented which has been found effectual in both obstetrical and general surgical cases. The latter will form a separate communication.

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## OBSERVATIONS ON CORONARY THROMBOSIS.

### WITH A REPORT OF THREE RECOVERED CASES.

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ALTHOUGH several excellent general reviews of coronary artery thrombosis are available, they contain reports of but few cases which have been observed over a long period of time. For this reason, it is felt that an account of 3 recovered patients studied for from one to about four years after the attack and of 6 other patients observed from soon after the occlusion until death may be of interest. All 9 patients were males; the youngest was fifty-five and the oldest seventy-three years of age. Arteriosclerosis was the principal cause of the occlusion in all. None gave evidence of syphilis or of rheumatic fever. Four patients had had no preceding cardiovascular symptoms. Five, however, had had dyspnea, with or without palpitation; and 4 of these also had had anginal seizures. In one instance there was moderate myocardial failure at the time of onset of thrombosis. One patient is known to have had auricular fibrillation for at least two years and another for at least six months before the occurrence of coronary occlusion. These 2 cases are unusual inasmuch as previous reports indicate that coronary thrombosis rarely occurs in a heart with fibrillating auricles. Necropsy was performed on 3 of the fatal cases.

In all patients the diagnosis was based primarily on the presence of characteristic symptoms and physical signs, substantiated by laboratory and electrocardiographic findings. The presenting symptom in all was sudden, excruciating, substernal, precordial,



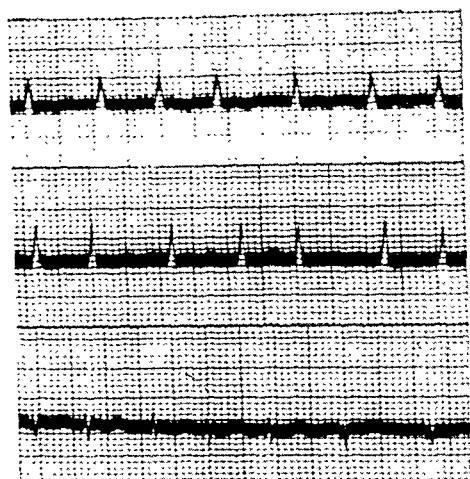
or epigastric pain, with or without radiation, lasting from a few hours to several days and accompanied by severe dyspnea. Nausea, vomiting, and extreme weakness usually attended or closely followed the onset. Physical signs of myocardial weakness were always present on admission. The heart sounds usually were distant and of poor quality; and disturbances of rhythm were common, particularly premature beats, gallop rhythm, auricular fibrillation, and varying degrees of heart block. Sudden changes in rhythm, often of short duration, frequently were observed. Persistent moist râles at the bases of the lungs were constantly found. The initial blood pressure generally was low, and the pulse weak and rapid. Three patients seen soon after the attack appeared to be in profound shock with subnormal temperature and ashen, gray, cold, moist skin. Enlargement of the liver was noted in 3 instances, but only 2 patients had peripheral edema on admission. The onset in the patient with antecedent myocardial failure presented no unusual features. A pericardial friction rub was heard in only one case.

Although patients coming to the hospital within thirty-six hours from the time of the first symptoms attributable to thrombosis, as a rule, had a subnormal temperature on admission, fever between 99° and 101° F. usually developed within the next twenty-four to forty-eight hours and persisted for two to ten days. Leukocytosis of from 11,000 to 21,000 cells per c.mm. was present in 8 cases, generally appearing within thirty-six hours of the onset, and continuing, as a rule, for some time after the temperature had become normal.

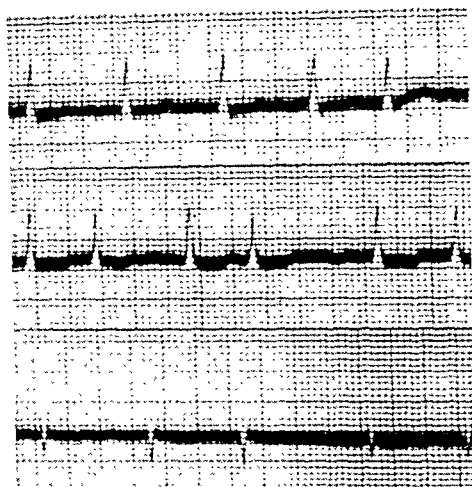
The occurrence of embolic phenomena in coronary thrombosis has been emphasized by Hamman.<sup>1</sup> Two of the 9 patients of the present series raised a large amount of bloody sputum, one, two days and the other, twelve days after the occurrence of occlusion. In both, hemoptysis was followed by marked increase in the degree of cardiac failure. None of the other 7 patients gave evidence of embolism at any time, although 2 showed old infarcts of the spleen at necropsy and 1 of these had, in addition, a small pulmonary infarct. It is known that in cardiac failure infarction may occur in the pulmonary or greater circulation without producing evident symptoms.

Blood pressure was recorded frequently in all patients. Not uncommonly a progressive fall in the systolic level was noted for several days after the beginning of the attack. Subsequent clinical improvement was accompanied by a rise of varying degree, extending to a distinctly high level in 2 patients; while with the occurrence of further attacks or the development of severe cardiac failure there was invariably a further fall.

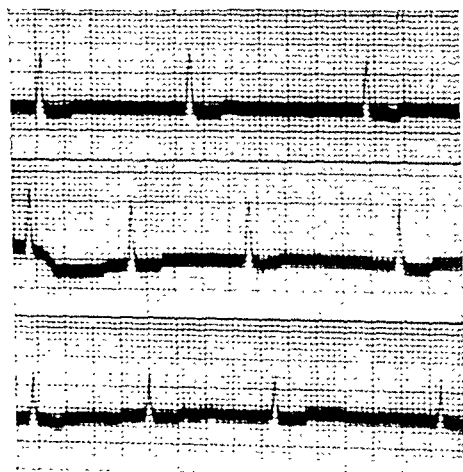
*The vital capacity* of the lungs was studied in 7 patients. All showed marked reduction below normal on admission to the hospital, and in 3 instances the initial reading was 1600 cc. or less. These



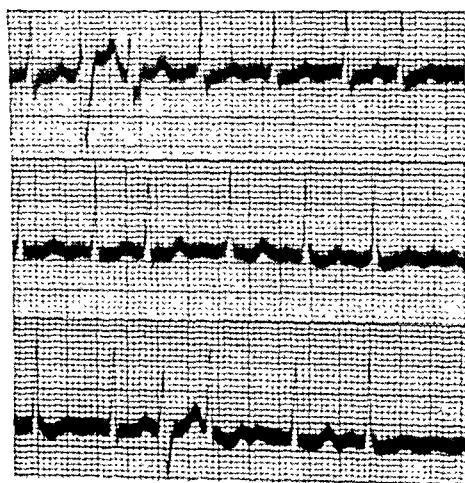
*A*



*B*

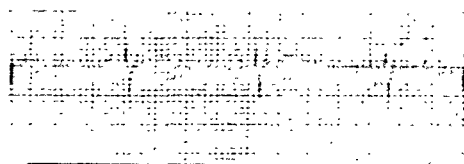


*C*

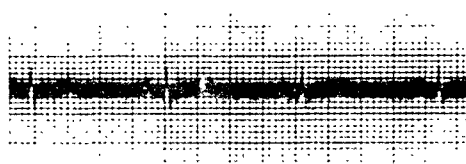


*D*

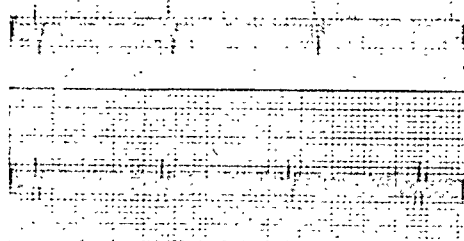
FIG. 1.—Electrocardiograms of Case I. *A*, record of October 15, 1924, ten days after onset of attack; *B*, record of October 17, 1924, showing increased amplitude of *Q-R-S* complexes; *C*, record of October 22, 1924; *D*, record of December 9, 1924.



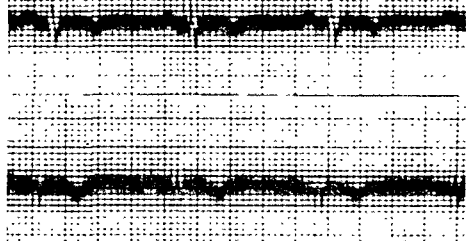
*A*



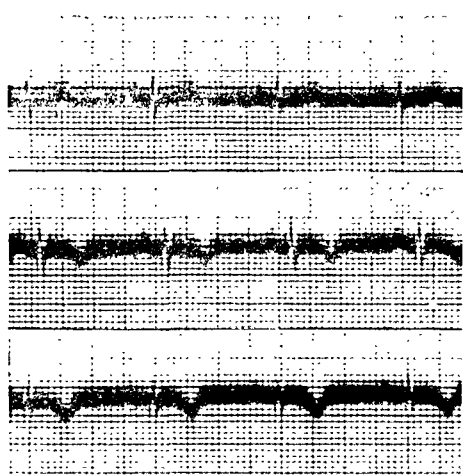
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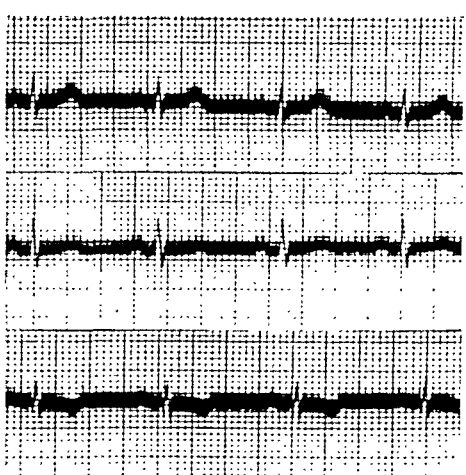
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*E*



*F*

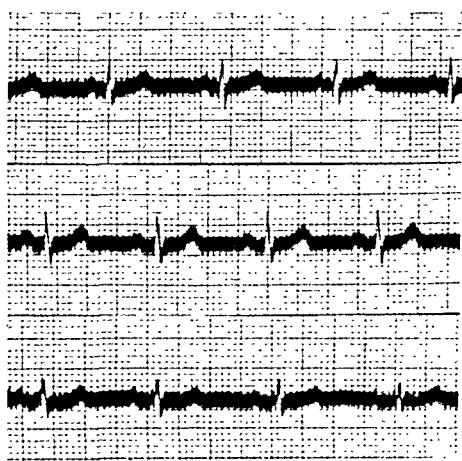
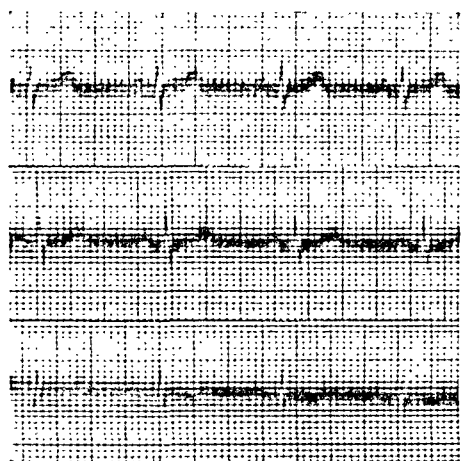
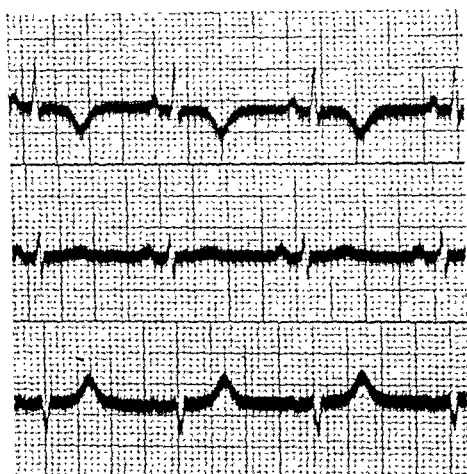
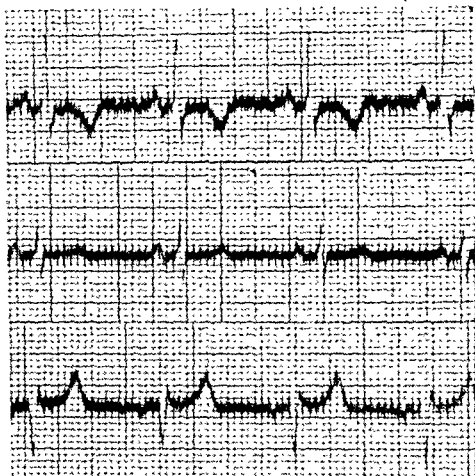


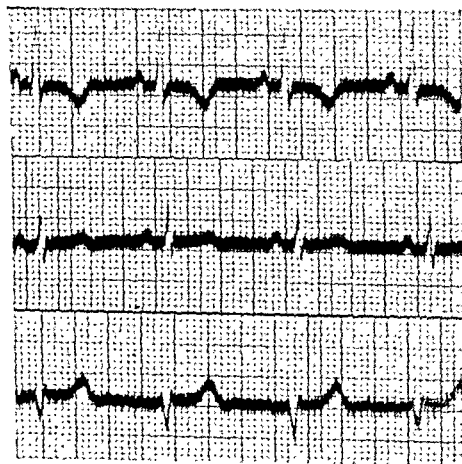
FIG. 2.—Electrocardiograms of Case II. *A*, record of March 2, 1926, the day after onset of attack; *B*, record of March 8, 1926, showing sharply-peaked negative *T* waves and upwardly convex *S-T* intervals in Leads II and III; *C*, record taken eight weeks after onset, showing *T* wave and *S-T* interval changes still present; *D*, record taken twelve weeks after onset, with *T-2* upright and *T-3* of diminished amplitude; *E*, record taken five months after attack, with *T-3* diphasic; *F*, record one year after attack, with *T-3* upright. Subsequent tracings show no further changes.



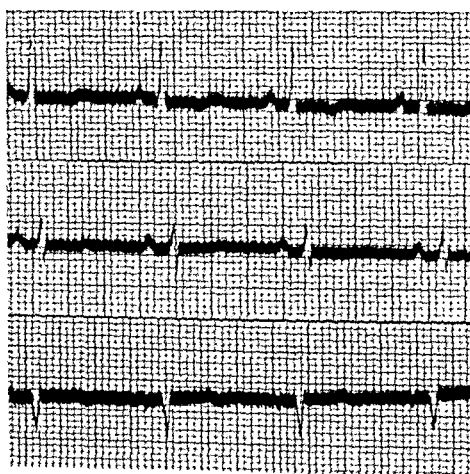
A



B



C



D

FIG. 3.—Electrocardiograms of Case III. A, record taken twenty-two days after onset of attack, showing coronary *T* wave in Lead I; B, record ten days later; C, record one week later; D, record taken three months after the attack; note the marked change in *T* wave in Leads I and III. Subsequent records show no further changes.



observations are of interest in view of the fact that so few peripheral signs of cardiac failure were present at the time. Clinical improvement usually was accompanied by an increase in vital capacity, while an unfavorable course was attended by further reduction.

**Fluoroscopic Studies.** Repeated fluoroscopic observations on the extent of cardiac excursion were made on 5 patients, 2 of whom recovered. In each instance the first examination was carried out within a few days of the onset and, without exception, showed marked diminution of cardiac pulsation. Two patients, one of whom recovered, presented only extremely slight, scarcely visible pulsations of the heart. The beats were so feeble indeed that the movements resembled a see-saw-like motion rather than true contractions. Subsequent examinations of patients who ultimately died showed no appreciable changes from the original findings, although in each instance there was temporary clinical improvement before the final decline. In the patients who recovered, however, there was a relatively rapid return of strong, visible, systolic pulsations coincident with clinical improvement, rising blood pressure, increased vital capacity, and improved quality of the heart sounds. Frothingham<sup>2</sup> has made similar observations on a patient who recovered.

Fluoroscopic examinations of the heart also were made on a number of patients with angina pectoris at a time when they were having no pain. Several of them, in whom the heart muscle obviously was very weak, showed definitely subnormal systolic pulsations. In none of these cases, however, did the diminution amount to the very faint see-saw movement observed in 2 of the patients with coronary thrombosis.

**Electrocardiographic Studies.** Electrocardiograms were taken on all the patients at frequent intervals. With one exception, the first record was always obtained within twenty-four hours of admission. Four patients had left ventricular predominance. All showed diminution in amplitude of the *Q-R-S* complexes accompanied, in many instances, by slurring, notching, or spreading. No relationship was observed between *Q-R-S* amplitude and changes in the clinical condition, blood pressure, vital capacity, or extent of cardiac excursion as observed fluoroscopically.

Each of the 6 fatal cases showed the *S-T* interval originating from a point on the *Q-R-S* complex above the isoelectric level, as described by Pardee.<sup>3,4</sup> Usually this feature was present in the initial record, although in one instance it did not appear until five days after the onset of symptoms. The upwardly convex *S-T* interval of Pardee<sup>5</sup> and the inverted, sharply-peaked *T* wave first described by Smith<sup>6,7</sup> were observed subsequently in 3 of these patients, the "coving" persisting, in each instance, for a variable time after this development.

An elevated origin of the *S-T* interval was not present in any

patient who recovered, but an upwardly convex *S-T* interval and negative, sharply-peaked *T* wave were observed in two (Figs. 2 and 3). In both instances these changes disappeared before the end of the third month.

**Subsequent Attacks.** Each of the 6 fatal cases showed on one or more occasions, without apparent cause, a sudden change in the clinical course. This usually consisted of recurrence or exacerbation of pain with sudden, conspicuous increase in dyspnea and other signs of myocardial failure. In the light of post mortem studies these sudden clinical alterations may be attributed either to extension of the existing thrombus or occurrence of fresh occlusion in another area. Of the 6 fatal cases, 4 died within three hours of onset of one of these episodes, and in the 3 with necropsy, the heart showed evidence of fresh and old infarction.

It is of interest that, in contrast to the fatal cases, 2 of 3 patients who recovered had no such attacks.

**Report of Cases.**—CASE I. J. R., a white male machinist, aged fifty-nine years, admitted October 15, 1924, complaining of epigastric and precordial pain, shortness of breath, and swelling of the lower extremities. For two years there had been dyspnea and palpitation on exertion with rather frequent attacks of angina pectoris. In May, 1924, the patient had been admitted with myocardial failure of *gradual* development, and at that time had auricular fibrillation. He improved rapidly with digitalis therapy and was discharged after five weeks. About October 1, 1924, he developed a severe, moderately productive cough with rapidly increasing dyspnea; and three days later, while doing light work, suddenly experienced severe, sharp, non-radiating epigastric and precordial pain with marked palpitation. With rest the pain quickly disappeared, but epigastric distress and a sense of abdominal distention persisted for over an hour. The following morning he attempted to finish his work, but in a few minutes the pain recurred with greatly increased intensity, accompanied by sudden, marked weakness, faintness, severe dyspnea, nausea and vomiting. Rest gave no relief. The pain persisted undiminished and became worse the next morning after a severe coughing spell with hemoptysis. Then after several hours, it diminished but did not entirely disappear during the ten days before admission to the hospital.

Examination showed a markedly orthopneic male in great distress. The skin was grayish; the lips were cyanotic, and the sclerae slightly icteric. The thorax was of the emphysematous type with signs of fluid at both bases. The vital capacity was 1700 cc. The left border of the heart was 12 cm. from the midline, and the apex impulse was neither seen nor felt. The heart sounds were very distant. No murmurs or friction rubs were heard. The apex rate was 154 per minute, absolutely irregular, with a pulse deficit of over 50. The radial arteries were moderately thickened. The blood pressure was 115 mm. systolic, 85 mm. diastolic. The liver extended 8 cm. below the costal margin, and there was marked edema of the lower extremities. The temperature was 99.2° F., and the leukocyte count 10,200 per c.mm.

With absolute rest in bed and digitalis, the pain disappeared in a few hours and the patient improved rapidly. He remained in bed for six weeks and left the hospital at the end of two months. The systolic blood pressure had risen gradually to 172 mm. and the vital capacity to 3100 cc.

Electrocardiograms were taken frequently and always showed auricular fibrillation, at times with varying numbers of ectopic ventricular beats. Four tracings are shown in Fig. 1. At no time were the *T*-wave changes described by Smith<sup>7</sup> and Pardee<sup>4,5</sup> observed.

The patient has been seen frequently since leaving the hospital and on two occasions has been readmitted with cardiac failure of gradual development. In August, 1928, he was feeling very well except for occasional short anginal attacks and slight dyspnea on exertion. He still had auricular fibrillation; the systolic blood pressure was 162 mm. and the vital capacity 2900 cc. There were no new electrocardiographic findings.

CASE II.—G. C., a white male, fire captain, aged fifty-eight years, admitted March 1, 1926, complaining of an almost unendurable sense of pressure in the chest. There had been no preceding symptoms of myocardial insufficiency. While walking on the afternoon of the day of admission, he had experienced a short anginal attack. Three hours later, while sitting in a chair, he developed excruciating epigastric and lower sternal pain, followed quickly by a sense of intense, gripping pressure over the entire chest. With this he became dyspneic, nauseated, extremely faint, and very pale. Neither walking nor lying down gave relief. After an hour he was unimproved and was brought to the hospital. On admission, his condition appeared critical. There was marked pallor; the forehead was covered with cold perspiration, and the expression was anxious. Respirations were shallow and moderately rapid. The thorax was somewhat emphysematous in type, and a few crackling râles were heard at the right base posteriorly. The heart extended 11.5 cm. to the left of the midsternal line. The apex impulse was neither visible nor palpable, and the heart sounds were scarcely audible. No murmurs or friction rubs were heard. The peripheral arteries showed moderate sclerosis. The radial pulses were regular, 92 per minute, soft, and easily compressed. Blood pressure was 105 mm. systolic, 75 mm. diastolic. The liver edge was not palpable, and there was no peripheral edema. The temperature was 98.2° F. and the white blood cell count, 8400 per c.mm.

In spite of two hypodermic administrations of morphin (gr.  $\frac{1}{4}$ ), pain persisted for over twenty-four hours. On the day after onset, the temperature was 98.8° F., and the leukocytes numbered 7000 per c.mm. The next day the white blood cell count was 14,000 per c.mm., the temperature 99.2° F., and the systolic blood pressure 98 mm. There was no fever after this, but leukocytosis persisted for several days. The patient was kept in bed for six weeks and was discharged without symptoms or signs of myocardial failure at the end of two months. The systolic blood pressure at this time was 118 mm.

Three days after onset, fluoroscopic examination showed only very slight, hardly visible see-saw movement of the heart shadow. Ten days later there was decided improvement in the cardiac excursion, and at a third examination shortly before discharge the contraction was definitely stronger.

Electrocardiograms were taken daily during the period of hospitalization and have been repeated at each return visit. The successive changes observed are shown in Fig. 2.

The patient has been seen frequently since leaving the hospital and, except for slight dyspnea and occasional mild low retrosternal oppression on exertion, has been free of cardiovascular symptoms. At present he is walking three to four miles daily, usually without discomfort. The heart sounds have remained of fair quality, and the systolic blood pressure has fluctuated between 120 mm. and 144 mm.



CASE III.—P. H., a white male, elevator operator, aged sixty-seven years, admitted April 17, 1927, complaining of persistent, severe, retrosternal pain. There had been moderate dyspnea on exertion for two or three years and quite frequent attacks of angina pectoris for one year. On the afternoon of April 16, 1927, while painting a fence, the patient suddenly developed severe, viselike, retrosternal pain radiating to the left shoulder and down the left arm to the elbow. He realized immediately that this was no ordinary anginal attack and later stated, "The pain was a thousand times as severe as any I had had before." Dyspnea, extreme weakness, nausea, vomiting, and profuse perspiration accompanied the onset. The pain was undiminished on admission twenty hours later. Examination showed a dyspneic, restless, apprehensive male. The face was ashen, and the lips were cyanotic. The thorax was moderately emphysematous with numerous crackling râles at either base. Vital capacity was 1600 cc. The heart extended 11 cm. to the left of the midsternal line. The apex impulse was neither seen nor felt, and the heart sounds were of poor quality. No murmurs or friction rubs were heard. The radial arteries were moderately sclerosed, and the pulses were of average quality, 80 per minute. Blood pressure was 130 mm. systolic, 70 mm. diastolic. The temperature was 98° F., and the leukocyte count 14,800 per c.mm.

Two hypodermic administrations of morphin (gr.  $\frac{1}{4}$ ) gave gradual relief, and six hours after admission the patient was quite comfortable. At this time he was showing short paroxysms of auricular fibrillation, an observation made several times in the first four days. On the day after admission severe epigastric and lower retrosternal pain recurred for several hours and was relieved only gradually by morphin. From this time, however, improvement was uninterrupted. Fever and leukocytosis persisted for ten days. The systolic blood pressure dropped slowly to 118 mm. during the first twelve days, but following this there was a gradual rise to 156 mm. at the end of two months. The vital capacity increased coincidentally to 2700 cc. Figure 3 shows the successive electrocardiographic changes observed.

Fluoroscopy of the heart four days after the onset showed moderate diminution of ventricular excursion with extremely weak right auricular contractions and only very slight aortic pulsation. Twelve days later ventricular contraction was somewhat stronger and aortic and right auricular pulsation had increased appreciably. One month later cardiac excursion seemed normal, and subsequent examinations have shown no further changes.

The patient has been seen frequently since discharge, and except for occasional short attacks of angina pectoris and slight dyspnea on exertion, his progress has been uneventful. The systolic blood pressure has dropped gradually to 136 mm., and the vital capacity has varied between 2600 and 2900 cc.

**Discussion.** The most common cause of cardiac infarction is thrombosis of the coronary arteries due to arteriosclerosis. Extensive thickening of the coronary arteries may occur without producing symptoms or signs of myocardial insufficiency, and the pain of coronary thrombosis may be the first indication of cardiovascular disease. The extent of myocardial infarction in a given case varies according to the size of the vessel occluded. Patients who have involvement of only a very small area may present very mild symptoms; and undoubtedly, as the disease becomes better understood, these cases will be recognized more often.

The striking symptoms and physical signs in cases with relatively extensive infarction usually are sufficient for diagnosis of the condition. In less severe cases, however, information obtained from other observations may be of great diagnostic assistance. The importance of fever, leukocytosis, and low blood pressure is generally recognized. Not uncommonly, as demonstrated in cases reported by Levine<sup>8</sup> and Gager,<sup>9</sup> there is a progressive fall in the systolic reading for several days after the onset. Diminished vital capacity of the lungs gives objective evidence of early circulatory failure; and, since enlargement of the liver and peripheral edema often are absent when the patient is first seen, this information frequently is of value. Marked diminution in cardiac excursion as observed fluoroscopically also may aid in recognizing the disease. The electrocardiogram shows significant features in a majority of cases. The occurrence of sudden changes in cardiac rhythm may aid in diagnosis, and embolism resulting from intracardiac thrombi occasionally is of assistance. The presence of a pericardial friction rub in a condition suggesting cardiac infarction makes the diagnosis certain, but unfortunately this sign is observed in only a small number of patients.

Favorable prognostic signs are progressive rise in blood pressure and vital capacity, improvement in strength of heart sounds, and increase in cardiac pulsation as observed fluoroscopically. Conversely, falling blood pressure after the first few days, decreasing vital capacity, and failure of the cardiac contractions to show improvement on fluoroscopic examination are unfavorable signs. Recovery from cardiac infarction is not attended in every instance by return of blood pressure to normal or high levels; many patients do well for years with a constantly subnormal reading. Repeated fluoroscopic examinations on a large series of patients probably would show likewise that many who recover, but with greatly diminished myocardial reserve, have permanently reduced cardiac pulsation. Symptoms and signs indicative of extension of infarction are to be regarded as of extremely serious import.

The early recognition of coronary thrombosis is of importance because, with proper management, the patient may recover and live for many years. The patients of this series were treated by being kept in bed for at least six weeks. During the first part of this time special nurses were provided, and the patients were not allowed to assist in any movement. Morphine in liberal doses was given for relief of pain, dyspnea, and restlessness. Digitalis was administered only to patients with persistent auricular fibrillation or peripheral congestive failure.

**Summary.** Three cases of coronary thrombosis with recovery and 6 cases terminating fatally have been studied. The recovered patients have been under observation for from one to about four years after the attack, and all at present are enjoying satisfactory health.

Soon after the occurrence of coronary thrombosis there is commonly a marked reduction below normal of the vital capacity of the lungs. This observation is of diagnostic value because many patients at this time show few peripheral signs of myocardial failure. The conspicuously small cardiac contractions observed fluoroscopically after coronary occlusion are likewise of diagnostic assistance.

Progressive rise in blood pressure and vital capacity and increasing cardiac pulsations observed fluoroscopically are favorable prognostic signs. Conversely, falling blood pressure after the first few days, decreasing vital capacity, and failure of the cardiac contractions to show improvement on fluoroscopic examination are unfavorable signs. Symptoms and signs indicative of extension of infarction are of very serious import.

The early recognition of coronary thrombosis is of importance because, with proper management, the patient may recover and live for years.

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### THE THERAPEUTIC INDICATIONS AND THE DANGERS OF THE INTRAVENOUS ADMINISTRATION OF SODIUM-PHENYLETHYL BARBITURATE (SODIUM LUMINAL) AND OTHER BARBITURIC ACID DERIVATIVES.

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SUFFICIENT time has elapsed since the introduction of the hypnotics of the barbituric acid series to allow one to formulate an opinion on their therapeutic value. The following discussion, which

is based on experimental and therapeutic observations, and upon a critical analysis of the literature, attempts to evaluate the problem of the rational application of these substances in a way to be valuable both to clinician and pharmacologist.

The intravenous administration of the barbituric acid derivatives has a distinct therapeutic value. This method of administration is, nevertheless, not without danger if used indiscriminately. A number of pharmacologic and therapeutic actions are identical in all the members of the series. For this reason, the general aspect of the problem will be presented before the discussion of the intravenous administration of the hypnotics.

**Definition and Synonyms.** The joint chemical, experimental and clinical studies of Fisher and von Mering<sup>1</sup> established in 1903 that

while barbituric acid,  $\begin{array}{c} \text{H} \qquad \text{CO-NH} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{H} \qquad \text{CO-NH} \end{array}$ , a derivative of urea  $\text{CO} \begin{array}{l} \text{NH}_2 \\ \text{NH}_2 \end{array}$   
and malonic acid  $\begin{array}{c} \text{H} \qquad \text{O-OH} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{H} \qquad \text{O-OH} \end{array}$ , is physiologically relatively inactive,

the substance obtained by replacement of the two hydrogen atoms by ethyl radicals is a powerful hypnotic in animals and man. This diethylbarbituric acid, commercially called veronal, or barbital, is a more efficient analgesic and hypnotic than chloral, paraldehyde and some other hypnotics. Since the introduction of diethylbarbituric acid into therapeutics, a large number of other barbituric acid derivatives have been prepared by substituting one or both hydrogen atoms with alkyl, cyclic and with a number of other radicals. The possibility of the number of these chemical substances is obviously unlimited. For this reason, under the disguise of various trade names, new therapeutic agents are continuously being introduced by commercial chemical and pharmaceutical houses. Specific claims for the therapeutic superiority of each of these hypnotics are made, although the main action of these substances is highly similar. Physicians are often misled by the different sounding trade names, and often, after discarding one preparation as unsuitable for a certain purpose, take up another with renewed hope. The following are the most widely used barbituric acid derivatives: Diethyl barbituric acid (*veronal* or *barbital*); sodium salt of diethyl-barbituric acid (*sodium veronal*; or *medinal*); iso-amyl-ethyl barbituric acid (*amytal*); iso-allyl-propyl barbituric acid (*allonal*); calcium-ethyl-iso-propyl barbituric acid (*ipral*); n-butyl-ethyl barbituric acid (*neonal*); cyclohexenyl-ethyl barbituric acid (*phanodorn*); phenyl-ethyl barbituric acid (*luminal*) and its sodium salt, *sodium luminal*.

All these names are synonyms for substances which are closely related chemically, in their pharmacologic and therapeutic action.

**The Pharmacologic Effects in Animals.** If an analgesic or hypnotic dose of any member of the barbituric acid series is administered to dogs, cats, rabbits, or other mammals, the main effects may be summarized as follows: Following the lapse of a period of time, varying mainly according to the channel of administration, the gait of the animal becomes ataxic. Simultaneous with this, excitement may manifest itself occasionally in purposeless struggle, rage, muscular tremor and rigidity. The animal may fall rather suddenly into superficial sleep, shortly to awaken again with excitement. With the onset of deeper sleep, the respirations become slow, occasionally rapid. Periods of Cheyne-Stokes respiration may occur. The cardiac rate is increased. The blood pressure as a rule falls but slightly (10 to 30 mm. of Hg). The peristaltic movements of the gastrointestinal canal stop, as observed under the fluoroscope. The sympathetic centers may also respond partially, provided the sleep is not too deep. The body temperature falls rapidly. The parallelism between the depth of sleep and degree of fall in body temperature is not always strict. In contrast to man, I have never observed rise in the temperature following the administration of barbituric acid derivatives in animals.

Marked fluctuation in the depth of sleep in the same animal, as well as individual variations between different animals are common. A number of factors is responsible for these variations. It was repeatedly observed that animals in dark, quiet rooms go to sleep sooner and after a smaller dose than those tied to a board. Motor or sensory excitement acts antagonistically to the effects of the barbituric acid derivatives. Reversely, a depressed state of the central nervous system acts synergistically. It was shown in a previous investigation<sup>2</sup> and in additional experiments<sup>3</sup> that morphin experimentally produced increased intracranial pressure, and other agents causing respiratory depression act synergistically with the barbituric acid derivatives in producing depression of the respiratory center.

If a fatal dose of the hypnotic is administered, death may result from paralysis of the respiratory center, or may follow a vasomotor collapse with complete loss of heat regulation.

The barbituric acid derivatives may reach the seat of their action through a number of channels of administration. The most frequent methods of administration are the oral, intraperitoneal, intramuscular and intravenous routes.

The onset of sleep may be almost instantaneous following the sudden intravenous injection of about 60 to 70 per cent of the fatal dose. If the injection is slow, however, the excitement may be identical with that observed after oral administration. Eddy<sup>4</sup> observed that the first evidence of action manifested itself in twelve to eighteen minutes after the oral administration of various barbituric acid

derivatives. In my experience, the stage of excitement is more marked with veronal than with amytal and allonal.<sup>5</sup>

**Toxicity and Dosage of the Members of the Barbituric Acid Series.** The analgesic and hypnotic, as well as the minimal fatal doses of the several derivatives vary considerably when these doses are expressed in actual amounts. It is of the greatest significance, however, that when the analgesic and hypnotic doses are expressed in percentage of the minimal fatal dose, the latitude between the hypnotic and fatal dose is essentially the same. Eddy observed that to induce hypnosis 50 to 60 per cent of the fatal dose of the members of the series he studied had to be administered. I have noted that 60 to 80 per cent of the fatal dose was essential to produce uniform sleep when animals are tied to a board, although 30 to 50 per cent of the fatal dose induced sleep in animals placed in their cages after injection. It was observed that the relative toxicity of veronal, amytal, allonal and luminal is essentially the same when administered intraperitoneally, or intravenously slowly.

**The Pharmacologic Effect and the Toxicity of the Barbituric Acid Derivatives in Man.** In man, as in animals, the barbituric acid derivatives act as sedatives, analgesics or hypnotics, depending on the amount administered. The toxic effect in man can be studied best on patients who take these drugs accidentally or intentionally. The following description of the pharmacologic effect of the barbituric acid derivatives is based on personal observation of patients, as well as on an analysis of the records of 135 patients admitted to the Boston City Hospital between 1910 and 1928, with acute poisoning due to veronal, luminal and allonal. It is certain, as has also been suggested by Caussade and Tardieu,<sup>6</sup> that the more important toxic reactions of individuals to the various members of the series are essentially the same.

The earliest manifestation of the drug effect is slight confusion with a heavy, dull sensation in the head and ataxia. Difficulty in swallowing, disturbed sense of smell and speech disorders may develop early. Occasionally nausea, vomiting and generalized excitement occur. With the onset of sleep, the rate of respiration usually is reduced and Cheyne-Stokes respiration may develop. If the sleep is deep and of longer duration the respiration is usually rapid and rather superficial. The heart rate is moderately increased and blood pressure slightly lowered (10 to 30 mm. of Hg). The reflexes are unchanged in moderate intoxication. The body temperature may be maintained; more often, however, there is a rise in temperature. A fall in temperature is also observed, but rarely in contrast to the usual occurrence in animals. The kidney function may be disturbed occasionally, as manifested by the presence of albuminuria, oliguria, and less often, anuria.<sup>7</sup> Colored vision, nystagmus, ophthalmoplegia, cardiac pain or a sensation of oppression in the thorax, bradycardia, decubitus, and permanent nerve injury are rarely observed manifestations.

In cases with fatal termination, marked cyanosis, moist skin, rapid, shallow respiration, very low blood pressure and rapid, thready pulse are noted. It is of interest that in two fatal cases of veronal poisoning the deep reflexes were present as late as four and six hours before death. The direct cause of death is usually either pulmonary edema or bronchopneumonia, with final paralysis of the respiratory center. The rise in temperature often develops before there is obtained either clinical or Roentgen ray evidence of bronchopneumonia. The white blood cells are normal until the onset of bronchopneumonia, when they usually increase in number.

Skin eruptions may be absent even upon fatal poisoning, or may appear after administration of small analgesic doses. They are manifestations of idiosyncrasy, rather than of hypersensitivity.

The fatal doses of barbituric acid derivatives in man cannot be estimated with any degree of accuracy from the available accidental or suicidal fatal cases. Aside from the marked individual susceptibility to the action of the drug, the nature of the stomach contents, and the presence or absence of emesis at the early stage of absorption make it difficult to estimate the amount of drug absorbed.

Although occasionally death is reported after such small oral doses as 3 gm. and 6 gm., several patients recovered after 6 or 7 gm. of veronal.<sup>7</sup> Death followed with greater regularity the consumption of over 12 gm. of veronal, although I have seen recovery after the ingestion of 17 gm. It is fair to estimate that for man the fatal dose of veronal usually is from 10 to 15 gm.

The following summary presents a correlation between the amount of veronal taken and the effect. Only those patients are included whose statements were reliable, and they were corroborated with statements of properly informed persons.

#### EFFECTS OF VARIOUS TOXIC DOSES OF VERONAL IN MAN.

1.5 gm.	. . . . .	No effect.
1.5 gm.	. . . . .	Stuporous, answers questions.
3.0 gm.	. . . . .	Drowsy, disoriented, tendency to sleep.
3.0 gm.	. . . . .	Drowsy, disoriented.
4.2 gm.	. . . . .	Stuporous, ataxic, sleeps twenty-four hours.
4.3 gm.	. . . . .	Drowsy, sleeps twenty-four hours.
6.0 gm.	. . . . .	Deep sleep, reaction serious.
9.0 gm.	. . . . .	Coma, bronchopneumonia, death.
21.0 gm.	. . . . .	Death.

Toxic reactions from luminal are more seldom reported in the literature because it is less frequently used with suicidal intent.<sup>7</sup> It is fair to assume that 4 to 6 gm. of luminal taken by mouth may be fatal frequently. It is also certain that at times much smaller amounts may be fatal.

The estimated fatal dose of 10 to 16 gm. of veronal, and of 4 to 6 gm. of luminal indicates that in an average man of 70 kg. the fatal dose of veronal by mouth is about 143 to 215 mg. per kg., and the estimated fatal dose of luminal is about 57 to 85 mg. per kg. of body

weight. If one compares these amounts with the approximate minimal fatal dose of 300 mg. per kg. of veronal, and 140 mg. per kg. of luminal, in cats and dogs, it seems evident that man is more susceptible to veronal and luminal and probably to other barbituric acid derivatives, than some of the lower mammals.

**Intravenous Administration of the Barbituric Acid Derivatives and their Therapeutic Usefulness in Man.** Soluble preparations of any barbituric acid derivatives produce almost instantaneous effect in man when administered intravenously. If given intramuscularly the substance enters the blood stream in from five to thirty minutes. The subcutaneous injection of all members of the series causes irritation, and necrosis is apt to result. The symptoms and signs produced by intravenous application are identical with those observed after oral administration. A quantitative comparison of the therapeutic effects of the oral and intravenous administration of identical doses of sodium luminal in patients suffering from epilepsy indicates that the efficiency of the two channels of administration is approximately the same.

The intravenous and intramuscular administrations offer the advantage over oral administration of producing almost instantaneous effects, and as the variable factor of intestinal absorption is eliminated the dosage may be more efficiently regulated to the therapeutic need. In certain conditions, for example, in cocaine and novocain poisoning, this instantaneous action may be of life-saving importance. In the majority of conditions in which the barbituric acid derivatives have great beneficial influence, the gastrointestinal channel of administration is not available, because of an agitated state of the central nervous system. Under the following headings are given the more important conditions in which the intravenous application of barbituric acid derivatives has been attempted during recent years.

*A. The Problem of Inducement of Surgical Anesthesia.* Fredet,<sup>8</sup> in 1925, observed that the combined administration of equal parts of diethylbarbituric acid, allylisopropyl barbituric acid (sommifen) and morphin induce deep sleep and anesthesia. The exact technique of administration is as follows: 10, 15 or 20 mg. of morphin chlorid and 0.66 mg. to 0.75 mg. of scopolamin are administered subcutaneously. Twenty to forty-five minutes later 10 mg. per kg., or an average total of 0.70 gm. of the sommifen is injected intravenously. The patient sleeps within a few minutes after the administration of these barbituric acid derivatives, and the sleep is deep enough to allow the surgical operation to commence with the aid of a few inhalations of chloroform as soon as ten minutes after the injection of the sommifen. Without the aid of chloroform the narcosis and analgesia are insufficient to permit the undertaking of surgical procedures. Bumm<sup>9</sup> found that the intravenous use of "sommifen" is dangerous because of the occasionally observed hypostatic



addition, oxygen was freely administered and 500 cc. of blood were removed through venesection. Eberhard believes that this method of treatment should replace the present widespread use of the Stroganoff<sup>21</sup> treatment. In Eberhard's 57 cases the mortality rate of the mother was 5.97 per cent and that of the child 23.5 per cent.

**Epilepsy.** The beneficial effect of the oral administration of phenol barbital (luminal) in epilepsy was established in 1912. Wyler<sup>22</sup> observed that the intravenous injection of from 0.2 to 0.4 gm. of somnifen checked the status epilepticus in three instances. In epileptic patients Patterson, Damon and Levi<sup>23</sup> used routinely by intravenous injection 0.12 gm. of sodium luminal, which at two-day intervals was increased by 0.06 gm. up to the maximal single dose of 0.3 gm. Untoward effects were not observed in over one hundred injections. Aside from the oral administration, the intravenous or intramuscular administration of the barbituric acid derivatives is indicated in severe status epilepticus, which condition because of persistent seizures, is of imminent danger to the patient's life, and at the same time the gastrointestinal channel is not available for administration.

Luminal sodium has been administered intravenously in 12 patients who were in status epilepticus, with evidence of circulatory collapse and pulmonary edema. The status lasted from two to fifteen hours before the first intravenous injection was given. Gradually increasing doses were given at intervals of one-half hour in order to establish the minimal effective dose. The amounts which controlled the convulsions varied from 0.4 to 1 gm. In one case a larger dose was required. In general, the amounts necessary to control convulsions were proportional to the severity of the motor irritation of the central nervous system. Eleven of the patients recovered, one died after the convulsions were controlled. This patient's condition was critical before the administration of the luminal, and it is therefore impossible to determine whether or not the luminal was a contributing factor.

**Toxic Reactions due to Certain Local Anesthetics.** The observations of Hofvendahl<sup>24</sup> and Tatum, Atkinson and Collins and others<sup>25</sup> clearly show that veronal and luminal may prevent otherwise fatal experimental cocain poisoning in animals, including monkeys. Following these observations, Leshure<sup>26</sup> reported that while morphin alone, or combined with scopolamin, did not prevent the occasional toxic reactions due to local anesthetics, from 0.4 to 0.8 gm. of sodium veronal administered by mouth routinely before operative procedures with a local anesthetic was efficient to prevent toxic reactions. Williams<sup>27</sup> used 0.3 gm. of barbital two hours and one hour before the beginning of operations with local anesthetics. He also noted beneficial results. Martin<sup>28</sup> observed that the frequency and severity of toxic reactions due to novocain were considerably reduced in patients receiving 0.60 gm. of barbital the

night before, and one hour before surgical operation. Guttman<sup>29</sup> also has reported that the routine hypodermic administration of from 0.18 to 0.3 gm. of barbital reduces the frequency of toxic reactions following the use of novocain.

That the proper intravenous administration of the barbituric acid derivatives is useful, not only as a preventive agent when administered before the use of local anesthetics, but also when injected after an alarming toxic reaction develops following local anesthesia, is shown by the observations herewith recorded.

**Case Reports.** CASE I.—T. C., a white boy, aged sixteen years, entered the hospital with a crushed right hand, which was caught in a machine. Except for this local condition, the physical examination revealed no abnormal findings. He was much excited. The arm was shaved and scrubbed with soap and water. Novocain infiltration with a 2 per cent solution of novocain at the elbow was started. After 50 cc. of novocain were injected the patient developed instantaneous violent convulsions. The convulsions recurred at about one- to two-minute intervals. The convulsions could not be controlled by immediate administration of ether. These seizures lasted for over thirty minutes. The patient became increasingly cyanotic, and signs of pulmonary edema developed. The pulse rose to 140 and was thready. The rectal temperature rose to 102.5° F. The patient's condition was considered critical. Administration of oxygen failed to benefit the patient. The administration of ether was stopped. The intensity of convulsions increased.

Thirty-five minutes after the onset of the convulsions, the intravenous injection of sodium luminal (10 per cent solution) was started. In three minutes, 450 mg. were injected and convulsions stopped instantly. Cyanosis gradually disappeared and the cardiac action became stronger. The pulse dropped to 110 per minute within thirty minutes. The pulmonary edema cleared up. Two hours later the patient was conscious. The surgical operation with ether was performed uneventfully on the following day and the patient was discharged three days later.

From the observations it is very suggestive that the intravenously administered sodium luminal saved the life of the patient.

**Tetanus.** During the past three years we have administered intravenously a 10 per cent solution of sodium luminal in 5 cases of tetanus. All the patients were suffering from pain and showed generalized spasm of the musculature with recurrent convulsions. The presence of opisthotonus prevented the performance of spinal puncture necessary for therapy in 3 of the patients. The administration of sodium luminal was indicated both for the comfort and for the recovery of the patient. The oral administration was not practical. Because experience on animals and on other patients indicated that the maximal hypnotic effect of the drug manifested itself within a few minutes, the method of administration finally adopted was to inject the drug continuously at a rate of 20 mg. per minute. When the onset of sleep and muscular relaxation were noted the injection was stopped. It was observed that the amount necessary to produce muscular relaxation varied from 0.8 to 1.2 gm. Following the injection of such an amount of sodium luminal,

complete relaxation developed although the sleep was superficial and the patient responded to pinching of the skin. The beneficial effect of a single dose of luminal lasted for from two to four hours, depending upon the severity of the increased muscular tone and the convulsions. The second dose necessary to overcome the muscular spasm was smaller. The respiration usually became slow about twelve minutes following the injection, and it then returned to normal. The systolic blood pressure dropped an average of 20 mm. of Hg, the diastolic 15 mm. of Hg. The temperature was unchanged, or showed a further rise after luminal. Three of the five patients died, the other two recovered.

It is thought that these 3 patients were in such desperate condition that death was inevitable, and that luminal did not influence the outcome.

CASE II.—R. Y., a white woman, aged forty years, confessed chronic morphin addiction. A few days before admission to the hospital she took frequent doses of morphin subcutaneously without sterilizing the needle. Two days before her entry her neck became stiff and later gradually her entire body became "stiff."

When seen she was unable to speak because of the trismus. The expression of the face was typically that of *risus sardonicus*. There was a complete fixation of the jaw. The neck was stiff. The respiration was rapid, about 30 per minute. The heart rate was slightly increased. The systolic blood pressure varied between 90 and 106 mg. of Hg, the diastolic between 65 and 80 mm. of Hg. The extremities were rather rigid. The deep reflexes were hyperactive. Occasionally tonic convulsions were present.

The intraspinal administration of tetanus antitoxin was not possible because of the general condition of the patient.

At 7.23 P.M. slow intravenous injection of a 10 per cent solution of sodium luminal was commenced. In the following ten minutes 1.3 gm. were injected.

At 7.45 P.M. the patient's jaw and the entire body relaxed; the patient was able to speak and complained of sleepiness and the injection was stopped.

At 7.52 P.M. the patient went to sleep and her body became relaxed. She was not in coma, however, and on pinching the skin responded with defensive motions of the extremities. The respiration was 17 per minute with periods of apnea and the face was flushed. The cardiac rate was 100. The blood pressure was 90 systolic and 60 diastolic. The rectal temperature was 99.4° F.

At 8.35-36 P.M. a 10 per cent carbon dioxide and 90 per cent oxygen mixture was administered. Respiration became deep and regular, indicating that the respiratory center was not severely depressed. Blood pressure was 80 systolic and 60 diastolic. Cardiac rate, 78. Rectal temperature, 99° F. Reflexes diminished but present.

At 9.20 P.M., during administration of an alcohol rub, the patient awakened.

At 9.38 P.M. the patient resisted the subcutaneous injection of physiological salt solution.

At 10 P.M. sleep was very superficial but the patient was nevertheless completely relaxed. Blood pressure was 80 systolic and 60 diastolic; heart rate was 78.

At 11.45 P.M. the patient awoke, and muscular spasm returned. Sodium luminal, 0.5 gm., was administered again intravenously. The patient

relaxed and slept again. Following this second dose the patient slept with the exception of short periods until 9 A.M.

At 9 A.M. the patient was awake. She was able to speak. The neck was slightly resistant but not stiff. Physical examination revealed suggestive signs of bronchopneumonia. Blood pressure was 104 systolic and 80 diastolic; respiration, 44; heart rate, 130; temperature, 101° F.

At 10 A.M. muscular spasm was back. After slow intravenous administration of 0.500 gm. of sodium luminal the patient was completely relaxed and slept. For several minutes Cheyne-Stokes respiration occurred.

At 11 A.M. the patient was awake again. 0.500 gm. of sodium luminal was administered. Patient relaxed and slept superficially.

At 3 P.M. the patient relaxed. Blood pressure was 90 systolic and 60 diastolic; respiration, 46; heart rate, 135; temperature, 103° F. Patient perspired freely. Definite clinical evidence of consolidation of the lower lobe of the left lung was elicited.

At 8 P.M. the sleep was still superficial. Patient was becoming comatose. She was cyanotic, perspired freely, and respiration was regular, rapid, but not labored. There developed clinical evidence of pulmonary edema and circulatory collapse. Temperature was 103.6° F.

At 9 P.M. the patient died.

During her stay in the hospital the patient received 47,000 units of tetanus antitoxin.

In this patient 2.8 gm. of sodium luminal was required to overcome muscular spasm and to induce sleep for twenty-five hours.

**Cerebral Hemorrhage with Convulsion.** The prompt relief of convulsions occurring in patients with cerebral injuries due to trauma or to intracranial hemorrhage is of great therapeutic significance in checking the extent of permanent intracranial damage. Sodium luminal was administered in intravenous doses of from 0.5 to 1.5 gm. in 3 patients with convulsions due to traumatic injury of the skull, and to 4 patients who, as a result of arterial hypertension, developed cerebral hemorrhage. The convulsions in all 7 patients were promptly relieved. Two of the hypertensive and one of the patients with traumatic injury died, as a result of pulmonary edema and bronchopneumonia, following an increasing coma lasting for from eighteen to twenty-six hours.

**Persistent Hiccough.** Six-tenths to 1 gm. of sodium luminal failed to stop persistent hiccough, although the patients became drowsy and sleepy. Two of the patients developed persistent hiccough of two and three days' duration after surgical operation on the prostate, the other three during a course of bronchopneumonia. The fact that the hiccough occurred simultaneously with each respiration indicates that this reflex is closely related to the respiratory reflex, which cannot be essentially influenced with safe doses of sodium luminal. This does not rule out that hiccough of less severity may not be influenced by proper doses of intravenous luminal.

**Discussion.** From the evidence presented it is clear that the pharmacologic and toxicologic effects of the various members of the barbituric acid derivatives are, with slight variations, the same in animal and in man. One of the most striking differences is the effect on the heat regulation. The different members of the series produce essentially identical effects in man, the existing differences

concern the intensity of excitement preceding the sleep and the persistence of action. Although the effective analgesic and the fatal dose vary considerably with the different members, there is a fairly uniform relationship between the analgesic, hypnotic, and fatal doses of different members of the series of the barbituric acid derivatives. In cats the analgesic effect was absent up to and including the administration of 30 per cent of the average fatal dose of a number of the members of the barbituric acid series. To produce stupor amounting to anesthesia at least 50 per cent of the average fatal dose was required. It is estimated that the fatal dose of sodium luminal in man is 3 to 4 gm.; the minimal amount producing sleep and moderate anesthesia varies from 0.7 to 1.5 gm. This indicates that 23 to 37 per cent of the fatal dose in man produces sleep and moderate relaxation and partial anesthesia. Man is therefore more sensitive to the toxic effect of the barbituric acid derivatives than animals, and in addition, a slightly lower percentage of the fatal dose is effective to produce analgesia and hypnosis. If Keeser's<sup>30</sup> observations are correct that the brain tissue has a special affinity for barbituric acid derivatives, then the relatively large bulk of the human brain may be one of the factors in producing this increased susceptibility.

Among the conditions determining the marked individual variations in the analgesic and fatal doses, the intensity of the afferent impulses to the central nervous system and excitability of the central synapses play a most fundamental rôle. Pain, sympathetic excitement, worry and fever act antagonistically to the effect of barbituric acid derivatives; while central depression is synergistic and, therefore, makes the patients susceptible to the depressant effect of the barbituric acid. As the clinical determination of the state of the central nervous system is not possible with any degree of accuracy, the effective use of the barbituric acid derivatives without individual consideration of the patient is not possible without incurring considerable danger.

Just as the dosage to produce a certain effect depends on the stage of the central nervous system, so also the persistence of action varies. Continuous sleep of over twenty-four hours' duration was observed after a single intravenous administration of 0.5 gm. to an epileptic patient, in whom the agitated state of the central nervous system was only temporary. On the other hand, the effect of 1.5 gm. of sodium luminal may last but about three hours in a patient with tetanus, in whom the abnormal impulses are persistently active.

Because of the marked variation in the effective dose, as well as in the persistence of action, the amount administered should be regulated for each patient. The routine dosage should be guided by the behavior of susceptible individuals. As the effect of the intravenous administration manifests itself almost instantaneously, and as the maximum effect, at least with luminal, is reached within from five to fifteen minutes after the injection, it seems advisable to

inject a 10 per cent solution of sodium luminal at a rate of about 50 mg. per minute, until the desired effect is obtained. The initial dose, however, should not exceed 1.5 gm. in an average adult.

With every therapeutic dose of barbituric acid derivatives sufficiently large to produce deep and persistent sleep, there is a potential danger of fever, circulatory collapse, secondary hypostatic congestion of the lungs, bronchopneumonia, and occasionally lobar pneumonia. The danger of these toxic manifestations increases considerably if an attempt is made to maintain hypnosis for several days, as has been attempted by investigators in certain types of psychosis. Bronchopneumonia or lobar pneumonia may develop during the period of recovery from the drug effect, and it may run a usual course after the patient has recovered from the direct effect of the hypnotic.

A comparison of the therapeutic efficiency of the barbituric acid derivatives with that of morphin, ether, chloroform, and nitrous oxid in various pathologic conditions suggests a different mechanism of action. The barbituric acid derivatives often influence functions of the central nervous system on which ether and morphin have no or only slight effect. The fact that the hypnotic effect of the members of the barbituric acid series is maintained or even increased after decerebration;<sup>30</sup> that disturbances in certain medullary functions may occur early and before the onset of sleep; and finally that these hypnotics are preëminently effective in abolishing the effect of cocain and novocain, substances which have specific action on the medulla and midbrain; all indicate that the hypnotics of the barbituric acid series have a specific affinity, influencing the functions of certain centers of the midbrain and medulla.

Observations both in animals and in man clearly show that severe motor disturbances may develop as a result of administration of the barbituric acid derivatives before there is an appreciable dulling of the sensory system. This also indicates that the gaseous anesthetics cannot be replaced by barbituric acid derivatives, and that the indications for their use are different. Ether, chloroform and other volatile anesthetics are more efficient analgesics than are the barbituric acid derivatives. On the other hand, the latter may be more effective than the former in certain motor excitement such as convulsions, increased muscular tone and emesis.

**Summary.** 1. The evidence presented herein suggests that man is more susceptible to the barbituric acid derivatives than animals, and that in man a relatively smaller percentage of the fatal dose produces analgesia and narcosis.

2. Marked individual variations exist in the response of patients to identical doses. The state of the central nervous system is one of the important factors which determines the variations in the intensity of effect, and in the persistence of action. Sensory and motor excitement act antagonistically, while depression acts synergistically with the barbituric acid derivatives.

3. Sodium luminal injected intravenously in doses of from 0.4 to 1.2 gm. at a rate of 50 mg. per minute in a 10 per cent solution stops convulsions, produces muscular relaxation, and induces sleep with considerable regularity. The narcosis even after such large doses may be superficial and the analgesic effect may be only partial. The effect of a single dose may last as long as twelve hours.

4. In certain patients with severe status epilepticus, eclampsia, grave toxic reactions from local anesthetics, convulsions due to cerebral hemorrhage or with tetanus the intravenous administration of sodium luminal and other barbituric acid derivatives is of distinct therapeutic value.

5. The routine use of the intravenous hypnotic dose of the barbituric acid derivatives for surgical anesthesia, or for the inducement of sleep of days' duration in certain psychoses is dangerous.

6. The mechanism of the action of the barbituric acid derivatives is different from that of ether, chloroform, and nitrous oxid. These anesthetics usually cannot be replaced by the barbituric acid derivatives. The hypnotics of the barbituric acid series have marked inhibitory influence on certain medullary and midbrain centers.

7. The dose administered to a patient should be determined by the individual behavior of the subject during the slow intravenous administration of the hypnotic. In the pathologic conditions discussed the intravenous administration of large sedative or hypnotic doses should be administered only if the condition of the patient is critical, and other measures which are just as efficient and more safe are not available. It should be remembered that a hypnotic dose of any barbituric acid derivative entails potential danger for the patient.

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## AN INTRATRACHEAL METHOD FOR PROLONGED ARTIFICIAL RESPIRATION.

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WHEN artificial respiration is required for a few hours only, as in resuscitation after drowning the Schaeffer method is simple and efficient.<sup>1</sup> For prolonged periods the necessity of relays of attendants working constantly makes the application of the Schaeffer method difficult. Manual methods of artificial respiration have



been used without success in the treatment of the respiratory paralyzes of poliomyelitis and diphtheria. It is possible that the exhaustion of the patient by the manipulation contributed to the fatal outcome.

Pharyngeal methods of artificial respiration, such as the pulmotor, have many disadvantages. The control of the intrathoracic pressure is difficult; vomitus and saliva may be forced into the lungs; air may be forced into the stomach.

Meltzer, in 1910, suggested, for clinical use, continuous intra-tracheal insufflation or as he called it "continuous respiration without respiratory movement."<sup>2</sup> In his method a catheter is passed into the trachea and the lungs are distended by air under constant pressure. The lungs are allowed to collapse by a complete interruption of the air current two to four times a minute. The method is based on the theory that the composition of the alveolar air can be changed by diffusion from the trachea through the distended bronchioles. The continuous air current accomplishes an important secondary result: the uninterrupted flow of air out of the larynx prevents saliva and vomitus from entering the lungs.

We began our present work with the idea that the Meltzer method was satisfactory. Our first failures were ascribed to too high or too low air pressure. More careful experiments indicated that the cause of failure was inherent in the method. If prolonged artificial respiration was to be successful a new method had to be devised.

**Experimental Respiratory Paralysis.** Methods of artificial respiration were tested on cats whose respiratory center had been destroyed by pithing or paralyzed by drugs. Paralysis by drugs permits the study of complications after the animal has recovered from the toxic action of the drug. At first we used curare to stop respiration but found it unsatisfactory. Divided doses of amytal gave better results. The amytal required varied widely ranging from 120 to 255 mg. per kg. As soon as respiratory movements ceased, artificial respiration was instituted. About every two hours the artificial respiration was stopped for one or two minutes to ascertain if the animal would breathe naturally. Respiratory paralysis lasted from two and a half to twelve hours.

**Experiments with the Meltzer Method.** A technical difficulty of the Meltzer method is the necessity of placing the catheter opening 1 cm. or less above the bifurcation of the trachea. Attempts were made to pass the catheter until the bifurcation was felt and then to withdraw it 1 cm. In cats, the catheter slips into a bronchus so easily that it is impossible to feel when the bifurcation is reached. It was necessary to determine the ratio:

Length (in centimeters) of the cat

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Distance (in centimeters) from incisor teeth to bifurcation.

In 22 out of 29 cats the ratio was fairly constant, 2.3. In 75 per cent of cats therefore,  $\frac{\text{length of cat}}{2.3} = \text{the distance that the tracheal}$

catheter must be inserted in order to lie 1 cm. or less above the bifurcation. In the remaining 25 per cent the incorrect position of the catheter caused failures. In the 22 experiments in which the catheter was properly placed the Meltzer method was sometimes successful. However, frequent failures occurred. Several animals died of circulatory collapse apparently due to the continuous high intrathoracic pressure. Two cats died of distention of the stomach with air, a complication described by Meltzer. In none did the method maintain life for more than five and a quarter hours. Cats with the respiration paralyzed by drugs either resumed natural breathing before the end of five and a quarter hours or they died. Pithed cats died before the end of four and a half hours.

These difficulties of the Meltzer method suggest why it has never come into common use. The following new technique has been devised which overcomes the difficulties and retains the advantages of the Meltzer method.

**The New Method.** Our method makes use of an intratracheal catheter. It differs from the Meltzer method in that the lungs are expanded every four seconds by air under pressure, then allowed to collapse and remain collapsed for three seconds. The alveolar air is changed, as in natural respiration, by movement of the lungs. During the stage of collapse the flow of air through the catheter continues but under very low pressure, not sufficient to expand the lungs. This produces an uninterrupted escape of air from the larynx.

**The Catheter.** A soft rubber catheter is introduced into the trachea through the larynx. With cats this is done by direct laryngoscopy using a urethral endoscope. In contrast with the Meltzer method it is not essential that the catheter lie at the bifurcation. It may lie anywhere in the lower half of the trachea. The catheter has two openings to insure patency under all conditions. For cats of 2 to 4 kilograms No. 14 Fr. is satisfactory. For larger animals a No. 16 Fr. is preferable. The relation between the size of the catheter and the size of the larynx is unimportant. The catheter is connected with the special respiration pump.

**The Intermittent Expanding Pressure.** Every four seconds a current of air under pressure is passed through the catheter for one second. This expands the lungs. The pressure is adjusted until the chest expansion is the same or slightly less than in normal breathing. The pressure does not develop suddenly but rises gradually, thus avoiding undue strain on the lung tissue. The pressure is measured by a mercury manometer and it is the same for animals of a size if the same size catheter is used. With a larger catheter a lower pressure produces the same effect.

*The Constant Pressure.* During the interval between expansions, the inflow of air is not stopped entirely. A constant stream of air passes through the catheter into the trachea and out of the larynx. The pressure of this stream is low enough to allow complete collapse of the lungs. The purpose of this constant stream of air is to prevent any saliva or vomitus from passing into the lungs.

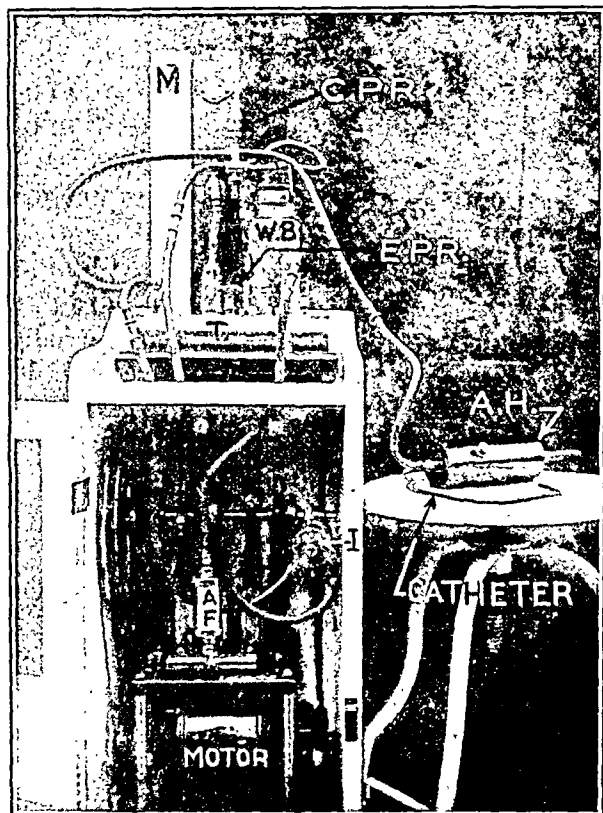


FIG. 1.—Apparatus for prolonged artificial respiration. The air passes from the motor-driven pump through the air filter *AF* to the tank *T*. From the tank the air may pass into the water bottle in two ways. Either through the direct connection controlled by the constant pressure valve *CPR*—or through the interrupter *I* which opens at intervals. The pressure of the latter air current is controlled by the expanding pressure regulator *EPR*. From the water bottle *WB* the air passes through the air heater into the catheter. A side-arm connects the manometer *M*.

**The Apparatus.** The apparatus<sup>1</sup> consists of several parts. There is a motor driven three-piston pump connected with a small tank (Figs. 1 and 2). Between the pump and the tank is an air filter (*AF*) which removes any coarse dust particles or oil. There are two connections from the tank to the tracheal catheter. The intermittent expanding air current passes through the interrupter (*I*). This is arranged to permit air to pass through every four seconds.

<sup>1</sup> The cost of the apparatus was defrayed by a grant from the Jeremiah Milbank Fund for the Study of Infantile Paralysis. Manufactured by C. M. Sorensen Co., Long Island City, N. Y.

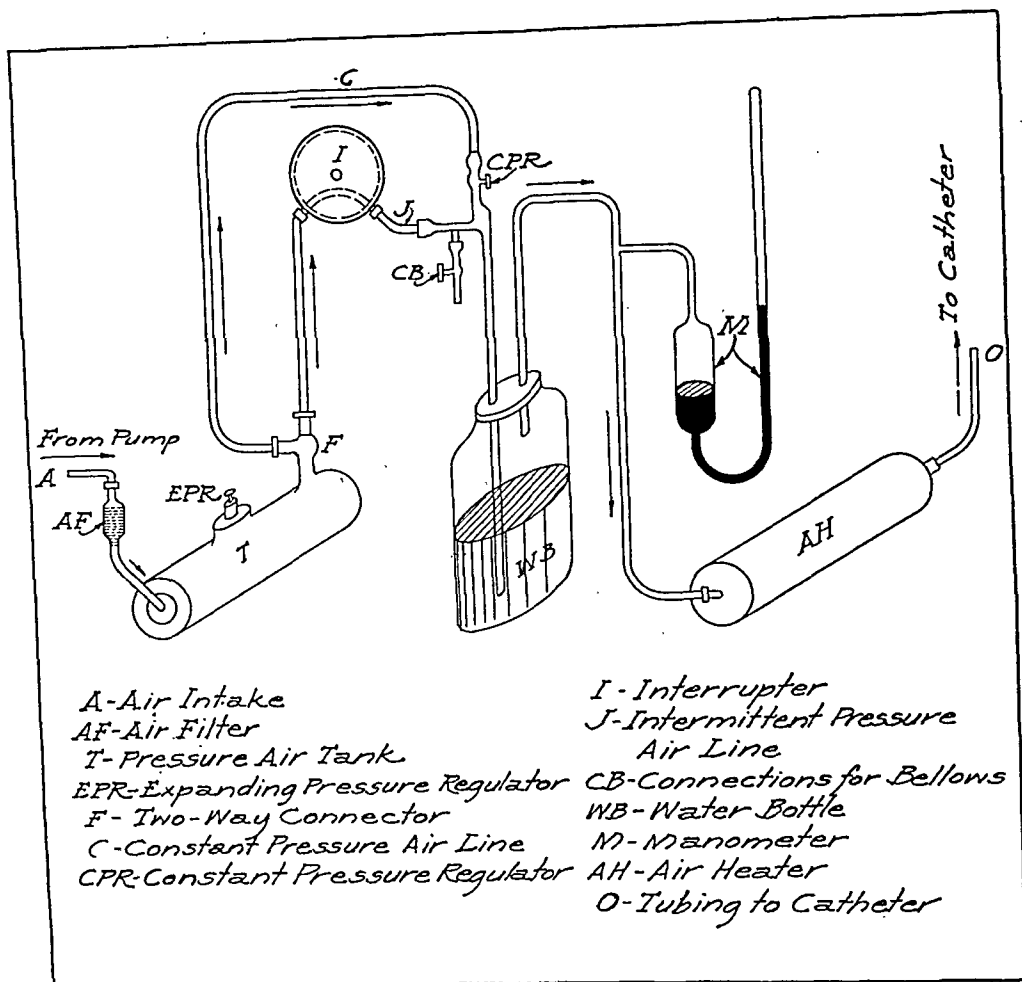


FIG. 2.—Diagrammatic representation of the apparatus.

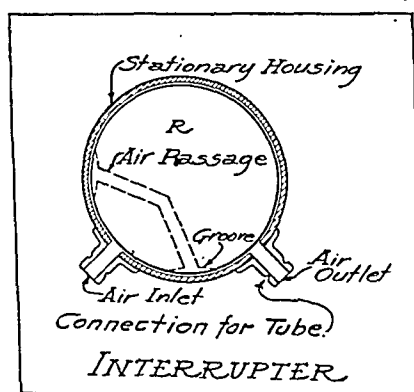


FIG. 3.—Detailed diagram of the interrupter.

The interrupter consists of a solid disklike core (*R*, Fig. 3) with a V-shaped passage through it. This disk revolves inside a stationary housing. The housing has two connections (air inlet and air outlet, Fig. 3) so fixed that once during each revolution of the disk they

are connected by the air passage. Small grooves on each side of the hole in the disk allow a small current of air to pass before the complete coincidence occurs. The effect is a gradually increasing air current. The maximum to which this pressure may rise is regulated by changing the pressure in the tank by means of a pin valve (*EPR*, Figs. 1 and 2).

A second air line (*C*) from the tank does not pass through the interrupter. The air flows through this connection at all times. The pressure of this constant current is regulated by means of a thread valve (*CPR*).

Both air currents pass into the water in the bottle (*WB*). This washes out dust particles which have escaped the air filter and saturates the air with water vapor. The air then passes through a heater (*AH*) and into the catheter. As it comes out of the catheter the air is at nearly body temperature and 50 per cent water saturated. It was found that the desired temperature and water saturation are more easily obtained by having the water bottle and heater in separate units.

The water bottle is connected with the mercury manometer (*M*) for measuring the pressure of both the intermittent and the constant air current. It does not, of course, measure the pressure of the air in the lungs. Manometer readings are a control when raising or lowering the pressure.

Comparisons may be made of pressures used in different animals. The pressure may be adjusted before hand to a slightly lower level than that which will probably be used. After beginning the experiment, the pressure is raised until the chest expansion is slightly less than in normal breathing.

**The New Method in Decerebrated Pithed Cats.** The new method of artificial respiration was uniformly successful in cats with the respiratory center destroyed by pithing. Although we did not continue any experiments more than twelve hours, the indications were that the animals could have been kept alive much longer. When it was decided to terminate an experiment, the pump was stopped and the animal allowed to die of asphyxia. Postmortem examination showed injection of the trachea. The lungs were normal. The following protocol illustrates this group of experiments:

EXPERIMENT NO. 44, APRIL 21, 1928. LENGTH OF CAT, 48 CM.

Time.	Heart.	Temperature.	Remarks.
8.40	105	..	{ Catheter passed 19.5 cm. and animal pithed. Artificial respiration by the new method.
8.55	120	39.2	
10.0	210	37.8	
11.05	170	37.6	
12.05	152	38.4	
2.0	168	38.2	
4.10	174		
6.0	160	38.6	{ Artificial respiration stopped. Cat allowed to die of asphyxia.
7.55	168	38.2	

**Comment on Experiment No. 44.** The respiratory center was destroyed by pithing and decerebration. The new method of artificial respiration was used for eleven and a quarter hours. The condition of the cat was satisfactory throughout the experiment. The cat was allowed to die of asphyxia; the catheter was left *in situ* and the thorax was opened.

The catheter was connected with the artificial respiration apparatus. At intervals of four seconds the intermittent air pressure caused good expansion of the lungs followed by collapse. The constant air pressure caused no expansion whatsoever, evidenced by the fact that there was no further collapse when both air currents were turned off. The trachea was slightly injected. The lungs and other organs were apparently normal.

**The New Method; Respiration Paralyzed by Drugs.** The catheter was inserted into the trachea and then the respiratory center was paralyzed. When there was no longer any sign of natural respiration the catheter was connected to the respiration apparatus. The animals were kept alive until natural respiration returned. Then the catheter was removed. In order to ascertain whether there were any late complications the animals were observed from three to seven days.

One cat died of pneumonia three days after it had artificial respiration. Several cats in the animal room not subjected to any experimental procedure died at this time.

With this exception the animals took their food well and showed no ill effects after recovery from the drug. Three to seven days after the experiment they were killed. A complete postmortem examination with special reference to the trachea and the lungs showed no pathologic changes. The following protocol illustrates this group and shows the technic used:

EXPERIMENT NO. 46, APRIL 25, 1928. LENGTH OF CAT, 50 CM.  
WEIGHT, 2.5 KG.

Time.	Heart.	Temperature.	Remarks.
8.40	..	..	{ Amytal 120 mg. per kg. intraperitoneally. Catheter passed 19.5 cm. Stopped breathing. Artificial respiration started.
8.55	..	..	
9.0	126	36.2	
10.15	129	36.5	
11.30	140	37.2	
1.15	145	37.6	
2.30	160	38.0	
3.50	144	37.4	
5.0	136	37.2	
April 27	..	..	Respiration 20. Returned to cage.
May 1	..	..	Eating. Animal killed. Autopsy.

**Comment on Experiment No. 46:** Respiration was paralyzed with 120 mg. of amytal per kilogram of body weight. The new method of artificial respiration was successfully used until natural breathing returned—eight hours.

We tested for the return of function of the respiratory center several times by discontinuing the artificial respiration one to two minutes. After recovery from the drug, the animal appeared normal. To hasten recovery from the narcosis, caffeine was injected the day after the experiment.

After recovery from the drug, the animal appeared normal. It was observed for six days and then killed. The trachea was moist and normal. The lungs and other organs were normal.

**Criterion of the Return of Respiratory Function.** It is important to note that the animals did not breathe naturally as long as artificial respiration was adequate. After artificial respiration was stopped the apnea lasted, at times, as long as two minutes. We tested for the return of respiratory function by disconnecting the catheter for two minutes. The animal either breathed or the heart rate rose rapidly. If the heart rate rose, the catheter was again connected and artificial respiration resumed. The short period of asphyxia was apparently harmless. A better test for the return of function is to stimulate the respiratory center by distending the lungs a few times with air or oxygen containing 5 to 10 per cent carbon dioxide. If the respiratory center is functioning, the animal will breathe almost immediately.

**The Intrabronchial Pressure.** The thorax was opened in pithed decerebrated cats kept alive with artificial respiration. A cannula was inserted into one of the main bronchi and connected with a water manometer. The intrabronchial pressure of the expanding air current was 4 to 8 cm. of water. The constant air current which caused no movement of the lungs, produced an intrabronchial pressure of  $\frac{1}{2}$  to 1 cm. of water. When both air currents were disconnected there was no further collapse of the lungs. Although we know that 6 cm. of water is the pressure required for adequate expansion of the lungs, this measurement cannot be made before the end of the experiment. The only criterion as to how much pressure to use in a particular case is to compare the expansion with a natural respiratory movement, and raise the pressure high enough to approximate the natural expansion. This can be done very easily.

**Advantages of the New Method.** 1. After proper adjustment no manipulation of the patient is necessary; the artificial respiration proceeds automatically.

2. Saliva and vomitus are not forced into the lungs, but are prevented from gravitating into the lungs.

3. The intratracheal catheter may be placed anywhere in the lower half of the trachea.

4. Excessive pulmonary pressure is guarded against. Sudden increase of the pulmonary pressure does not occur.

5. Circulatory failure is not likely to occur because the high intrapulmonary pressure is maintained for only a short time.

6. Distention of the stomach with air does not occur.

7. Feedings may be given by gavage.

**Clinical Application.** The method was used in two cases of poliomyelitis with complete respiratory paralysis. The patients were cyanosed, pulseless and showed no signs of any muscle movement when artificial respiration was begun. Normal color and pulse returned and were maintained in one patient for nine hours and in the second patient for twelve and a half hours; at the end of that time the heart stopped. It seems reasonable to assume that the respiratory paralysis in some cases of poliomyelitis may be transient as are some of the skeletal paralyses. If such is the case, artificial respiration should be maintained until the recovery of the center or death from circulatory failure. The clinical application will be reported in detail in another paper.

**Conclusion.** A new method of artificial respiration is described which has been used successfully in animals. Clinically it has been used in two cases and should be tried more extensively.

**NOTE.**—We are indebted to Prof. C. C. Lieb for the privilege of working in his laboratory and for his helpful suggestions.

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## REVIEWS.

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PRACTICAL MATERIA MEDICA. By CLAYTON S. SMITH, PH.D., M.D., and HELEN L. WIKOFF, PH.D., Department of Physiological Chemistry and Toxicology, College of Medicine, Ohio State University. Pp. 284. Philadelphia: Lea & Febiger, 1929. Price, \$3.25.

THIS book is intended primarily for the medical student. It contains concise summaries of the properties and preparations of important drugs, inorganic and organic, as well as sections dealing with toxicology and with prescription writing and incompatibilities. Structural formulæ are given with welcome frequency. The suggested laboratory exercises in connection with the various drugs are concerned chiefly with pharmaceutical preparation and assaying, but directions for chemical experiments with many drugs are given in the section on toxicology. The book contains the material for a comprehensive course in materia medica and toxicology, and is recommended to teachers of those subjects. C. S.

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DIABETIC SURGERY. By LELAND S. MCKITTRICK, M.D., F.A.C.S., Visiting Surgeon, Palmer Memorial Hospital; Assistant Surgeon, New England Deaconess Hospital; Surgeon to Outpatients, Massachusetts General Hospital; and HOWARD F. ROOT, M.D., Assistant Physician, New England Deaconess Hospital; Associate in Medicine, Peter Bent Brigham Hospital and Palmer Memorial Hospital; with a Foreword by DANIEL F. JONES, M.D., and ELLIOTT P. JOSLIN, M.D. Pp. 269; 79 engravings and 2 colored plates. Philadelphia: Lea & Febiger, 1928. Price, \$4.25.

NINE years ago, a well-known authority on diabetes in writing on the subject dismissed the surgical complications of the disease rather briefly, explaining that "they occupied much space in older textbooks but are becoming less numerous as diabetes is earlier diagnosed and better treated." The experience of the intervening years has, however, been quite different. While the mortality rate from diabetes throughout the country has actually increased, in the last few years, as recently pointed out by Dr. F. L. Hoffman, fewer and fewer of the deaths have been due to coma, thanks to insulin; on the

other hand, surgical conditions have accounted for a steadily increasing percentage of the fatalities. Prior to 1922, 9.8 per cent of Joslin's fatal cases were due to surgical conditions, while in the period 1925 to 1927 the surgical-death percentage was 71. This book is, therefore, a most timely one, and coming, as it does, from associates of Dr. Joslin, it represents the fruits of a large experience. Surgeons will, of course, read it; but the Reviewer wishes particularly to recommend it to internists and practitioners, for, "In most cases diabetic patients with gangrene die a surgical, not a medical death. This is usually due to neglect on the part of the patient, procrastination on the part of the family physician and, too often, delay on the part of the surgeon or internist."

R. K.

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THE MOBILIZATION OF ANKYLOSED JOINTS BY ARTHROPLASTY. By W. RUSSELL MACAUSLAND and ANDREW R. MACAUSLAND. Pp. 252; 154 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$4.00.

A MONOGRAPH presenting its subject in a concise manner and from the viewpoint of the surgeon. Written by one of the foremost exponents of the use of arthroplasty in the restoration of function with stability to ankylosed joints.

The treatise is thorough; the recommendations conservative; much of the material has appeared in various publications by the senior author.

G. W.

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CLINICAL PHYSIOLOGY (A SYMPTOM ANALYSIS) IN RELATION TO MODERN DIAGNOSIS AND TREATMENT. A TEXT FOR PRACTITIONERS AND SENIOR STUDENTS OF MEDICINE. By ROBERT JOHN STEWART McDOWALL D.Sc., M.B., F.R.C.P. (EDIN.), Professor of Physiology, King's College, University of London. With an Introduction by W. D. HALLIBURTON, LL.D., F.R.C.P., F.R.S., Emeritus Professor of Physiology, King's College, University of London. Pp. 383; 4 illustrations. New York: D. Appleton & Co., 1927.

In his preface the author defines the reason why he wrote this book.

"Some years ago it was my fortune to take an active part in the teaching of clinical medicine and, during that period, it was possible to study in some detail how far the average medical student was able to adapt his knowledge of the science of Physiology to his practical requirements. It was fully realized that the study of Physiology in its more scientific aspects was in every way desirable, but it was clearly seen that for the adequate appreciation of the signs and

symptoms of disease more was necessary than is normally taught by the physiologist or clinician. It is, for example, extremely difficult—indeed almost impossible from a study of ordinary textbook Physiology—for him to see why a cardinal symptom of cardiac disease should be breathlessness.

"This volume is an attempt to present some of the facts of physiology and their applications in general medicine in a form which fits in conveniently with pathologic and clinical teaching."

The author discusses briefly such phenomena as:

The venous pulse and the heart sounds, blood pressure, the effect of hemorrhage and allied conditions on the circulation, cyanosis and breathlessness, vitamins, growth, swallowing and digestion, formation and excretion of bile, etc. The Reviewer finds it necessary to criticize the extreme brevity with which some of the subjects discussed have been treated. However, there is a great deal of well written useful information, which should help the student and the practitioner better to understand the functional disturbances brought about by disease processes.

B. L.

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OLD AGE. THE MAJOR INVOLUTION. THE PHYSIOLOGY AND PATHOLOGY OF THE AGING PROCESS. By ALDRED SCOTT WARTHIN, PH.D., M.D., LL.D., Professor of Pathology and Director of the Pathological Laboratories, University of Michigan, Ann Arbor. Pp. 199; 29 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$3.00.

AN enlargement of the author's Carpenter Lecture before the New York Academy of Medicine, the thesis is developed that the involution processes of old age are essentially physiologic in nature. Thus Metchnikoff's orthobiosis is opposed on the one hand, and the various attempts at rejuvenation, on the other. The demonstration by Carrel's tissue cultures that even mammalian cells are potentially immortal is cursorily dismissed as an irrelevant pathologic process. To some people, however, there already exists support for believing that many of the phenomena of old age can with more reason be considered pathologic and therefore perhaps removable. Impressed, perhaps overimpressed, with the idea that the whole life process is "chiefly, or solely, for the attainment of one end that the species shall not perish from the earth," the author logically contemplates all postfertile ages with what philosophical equanimity he can muster, as part of the gradual process of decay. Analogies with plant life are obvious, but for practical human purposes at least, the inestimable achievements attained by individuals in the so-called involution period would better have received more attention and emphasis. Many will be surprised to learn that "un-

doubtedly the fourth decade brings the best results" in progeny and that "ideal ages for marriage are twenty-eight to thirty years in the male, and twenty-six to twenty-eight years in the female," even though the offspring alone is here being considered. The distinguished author is making a stoical and apparently successful effort to apply the last words of his book—Goethe's quotation: "Keine Kunst ist's alt zu werden, es ist Kunst es zu ertragen;" whether such an attitude will tend to retard our scientific knowledge of senility and the eventual happiness of the aged is, however, a different question.

E. K.

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THE TONSILS AND ADENOIDS AND THEIR DISEASES. By IRWIN MOORE, M.B., C.M. (EDIN.), Late Honorary Surgeon to the London Throat Hospital for Diseases of the Throat, Nose and Ear, Great Portland Street, and also to the Hospital for Diseases of the Throat, Golden Square, London, W. Pp. 395; 107 illustrations and complete bibliography. St. Louis: The C. V. Mosby Company, 1928. Price, \$6.50.

THIS is an eminently practical book on the diseases of the tonsils and adenoids. The anatomy, pathology and surgery, including the various methods of controlling hemorrhage, with many illustrations is clearly described. A complete chapter on tonsils, as a source of focal infection in systematic diseases with extensive references is noteworthy.

In it you will find the opinion and case reports of the best-known otolaryngologists in the world, with numerous reports of fatalities following tonsil and adenoid operation. The book is well written, and diseases of the tonsils and adenoids including the lingual tonsils are clearly described. This should be an excellent book for medical students, general practitioners and a reference for specialists.

D. H.

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PHARMACOTHERAPEUTICS. By SOLOMON SOLIS-COHEN and THOMAS STOTESBURY GITHENS. Pp. 1869. New York: D. Appleton & Co., 1928. Cloth. Price, \$15.00.

THIS is a treatise on drug therapeutics, but it is unique in several respects. It is written primarily for the clinician, and, therefore, contains details of preparations, mode of administration and of results to be expected, that are not found in books dealing with pharmacology. The discussions of pharmacological and toxicological features are more authoritative and up to date than is the

case with treatises on therapeutics. Of particular value are the sympathetic discussions of many agents which, because their employment rests wholly upon empirical observations, are given scant consideration in current works upon pharmacology. The history of each drug is sketched with unusual thoroughness. Newer remedies, such as chaulmoogra and ephedrin, are given adequate consideration, as are serums, vaccines, antigens, etc. This book contains information that is available in no other single work that is known to the Reviewer, and is highly recommended to experimenters as well as clinicians.

C. S.

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ANTENATAL CARE. By W. E. T. HAULTAIN, O.B.E., M.C.; B.A., M.B. (CAMB.), F.R.S.C.E., Senior Assistant Obstetric Physician to the Antenatal Department, Edinburgh Royal Maternity and Simpson Memorial Hospital; and E. CHARLES FAHMY, M.B. (EDIN.), F.R.S.C.E., Assistant Obstetric Physician, Antenatal Department, Edinburgh Royal Maternity and Simpson Memorial Hospital. With a Foreword by PROF. R. W. JOHNSTONE, C.B., M.A., M.D., F.R.S.C.E., Professor of Midwifery and Diseases of Women, University of Edinburgh. Pp. 108; 2 illustrations; 2 charts. New York: William Wood & Co., 1929. Price, \$2.25.

THIS small but meaty book is a description of the methods of antenatal practice of the Edinburgh school. The measures recommended are modern and coincide closely with the generally accepted teaching in the United States. The single criticism might be that no metric equivalents are given for the various pelvic and cephalic measurements. The therapy of various antenatal disorders, toxemias, syphilis and gonorrhea are detailed. This is an excellent manual for the prenatal clinic worker.

P. W.

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PROGRESSIVE RELAXATION. By EDMUND JACOBSON, A.M., Ph.D., M.D., of the Physiological Laboratory, the University of Chicago. Pp. 429; 69 illustrations and figures. Chicago: The University of Chicago Press, 1929. Price, \$5.00.

THIS serious study of rest has extended over a period of twenty years and a new method is given for the treatment of hypertension—a term preferred to neurasthenia unless actual exhaustion is present.

Through his muscle sense, the subject is taught to recognize tension by movements of the body that will cause contraction in any given part and with this fundamental knowledge, he proceeds to undo his own hypertension.

The treatments vary in duration, frequency and over the period of time employed.

Many conditions are cited as being greatly benefited and among others, hypochondria. Right here the author runs counter to accepted authority. The less a hypochondriac meddles with his body, the better. What he needs is to be guided away from himself—plenty of wholesome work and a hobby.

While the procedure appears to have merit, there is an unpleasant amount of fault-finding with other methods. An extensive bibliography is appended.

N. Y.

THE NOSE, THROAT AND EAR AND THEIR DISEASES. In Original Contributions by American and European Authors. Edited by CHEVALIER JACKSON, M.D., Sc.D., LL.D., F.A.C.S., Chevalier de la Legion d' Honneur; Chevalier del 'Ordre de Leopold, Professor of Bronchoscopy and Esophagoscopy in the University of Pennsylvania, in the Jefferson Medical College and in the Graduate School of Medicine of the University of Pennsylvania; Lecturer on Bronchoscopy and Esophagoscopy in the Women's Medical College of Pennsylvania and in Temple University, Philadelphia; and GEORGE MORRISON COATES, A.B., M.D., F.A.C.S., Professor of Otology, University of Pennsylvania Graduate School of Medicine; assisted by CHEVALIER L. JACKSON, A.B., M.D., Assistant in Bronchoscopy and Esophagoscopy, University of Pennsylvania and the Graduate School of Medicine, University of Pennsylvania. Pp. 1177; 657 illustrations and 27 inserts in colors. Philadelphia and London: W. B. Saunders Company, 1929. Price, \$13.00.

SUCH a volume on the diseases of the nose, throat and ear with so many distinguished and internationally known authorities has never been published before. European and American authorities under the supervision of the authors have written this complete book.

The anatomy, pathology, diseases and treatment, medical and surgical of the nose and sinuses with a complete chapter on sinuses in children and their diagnosis and complication with clear-cut illustrations is the last word.

Anatomy and diseases of the ear, including the surgery and complications of the mastoid operation with many beautiful illustrations cannot be improved upon at this time.

The chapter on the larynx which takes up four hundred pages, a book in itself, is a classic in its field and a most reliable guide for the laryngologist. The endoscopic views and drawings of Jackson are inimitable.

This book belongs to the highest type of medical writing, editing and publishing in this country. It is a credit not only to its authors but to its editors as well, and no otolaryngologist can afford to be without it.

D. H.

# BOOKS RECEIVED.

## NEW BOOKS.

*A History of the Medical Department of the United States Army.\** By COL. P. M. ASHBURN. Pp. 448. Boston and New York: Houghton, Mifflin Company, 1929.

*Stephen Hales, D.D., F.R.S.\** By A. E. CLARK-KENNEDY. Pp. 256; 14 illustrations. New York: The Macmillan Company, 1929.

*The Custom of Couvade.\** By WARREN R. DAWSON, F.R.S.E. Pp. 118; 1 illustration. Manchester, England: The Manchester University Press, 1929. Price, 7/6.

*Clinical Aspects of Venous Pressure.\** By J. A. E. EYSTER, B.Sc., M.D. Pp. 135; 7 illustrations. New York: The Macmillan Company, 1929. Price, \$2.50.

*The History of Hemostasis.\** By SAMUEL CLARK HARVEY, M.D. Pp. 128; 19 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$1.50.

*An Introduction to the Study of Physic.\** By WILLIAM HEBERDEN. Pp. 159; 6 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$2.00.

*The Physiology of Love.* By GEORGE M. KATSAINOS, Ph.D., M.D. Pp. 326. Boston: Privately printed, 1929. Price, \$4.00.

*Gonorrhea and Kindred Affections in the Male and Female.\** By GEORGE ROBERTSON LIVERMORE, M.D., F.A.C.S., and EDWARD ARMIN SCHUMANN, M.D., F.A.C.S. Pp. 257; 66 illustrations. New York: D. Appleton & Co., 1929. Price, \$5.00.

*Collected Papers of the Mayo Clinic and the Mayo Foundation, 1928. Volume XX.* Pp. 1197; 288 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$13.00.

Eighty-one papers are printed entire, 43 abridged, 72 abstracted and of 233 references only are given.

*Medical Department of the U. S. Army in the World War. Volume X: Neuropsychiatry.* Pp. 543; 3 illustrations. Washington: U. S. Government Printing Office, 1929.

*Medical Department of the U. S. Army in the World War. Volume III: Finance and Supply.* Pp. 935; 50 illustrations. Washington: U. S. Government Printing Office, 1929.

*Medical Department of the U. S. Army in the World War. Volume XII: Pathology of the Acute Respiratory Diseases and of Gas Gangrene following War Wounds.* Pp. 583; 312 illustrations. Washington: U. S. Government Printing Office, 1929.

*Osteomyelitis and Compound Fractures and Other Infected Wounds.\** By H. WINNETT ORR, M.D., F.A.C.S. Pp. 208; 54 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$5.00.

*Progressive Medicine, Volume II, June, 1929.* Pp. 389; illustrated. Philadelphia: Lea & Febiger, 1929.

\* Reviews of titles followed by an asterisk will appear in a later number.

- Diabetes Latente.* By DR. FELIX PUCHULU. Pp. 213. Buenos Aires: Talleres Graficos Ferrari Hnos, 1929.
- The Conquest of Cancer.\** By DANIEL THOMAS QUIGLEY, M.D., F.A.C.S. Pp. 539; 334 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$6.00.
- The Modern Dance of Death.\** By PEYTON ROUS, M.D. Pp. 51. Cambridge, England: Cambridge University Press, 1929.
- Pathologico-anatomical and Clinical Investigations of Fibro-anemonatosis Cystica.\** By CARL SEMB. Pp. 484; 37 illustrations. Oslo: Nationalbrukkeriet, 1928.
- Surgical Clinics of North America, New York Number, Volume IX, No. 3, June, 1929.* Pp. 299; 125 illustrations. Philadelphia: W. B. Saunders Company, 1929.
- Tumores Primitivos de la Pleura.\** By JOSE W. TOBIAS. Pp. 479; 60 illustrations. Buenos Aires: El Ateneo, 1928.
- Principles and Practice of Electrocardiography\** By CARL J. WIGGERS, M.D. Pp. 226; 61 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$7.50.
- The Life of Hermann M. Biggs, M.D., B.Sc., LL.D.\** By C.-E. A. WINSLOW, DR.P.H. Pp. 432; 35 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$5.00.

## NEW EDITIONS.

- Manual of Diseases of the Nose, Throat and Ear.* By E. B. GLEASON, M.D., LL.D. Sixth edition. Pp. 617; 268 illustrations. Philadelphia: W. B. Saunders Company, 1929.
- A careful revision with special attention given to the criticisms of teachers of otolaryngology.
- Clinical Laboratory Methods.* By RUSSELL LANDRAM HADEN, M.A., M.D. Third edition. Pp. 317; 73 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$5.00.
- A few new methods such as the Kahn precipitation test and the determination of indican in the blood have been added.
- Diseases of the Thyroid Gland.* By ARTHUR E. HERTZLER, M.D. Second edition. Pp. 286; 159 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$7.50.
- A Manual of Proctology.\** By T. CHITTENDEN HILL, PH.B., M.D., F.A.C.S. Third edition. Pp. 272; 86 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$3.50.
- Practical Chiropody.* By E. G. V. RUNTING. Third edition. Pp. 200; 21 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$3.00.
- A practical booklet containing much sound advice about small but very often troublesome matters.

\* Reviews of titles followed by an asterisk will appear in a later number.



# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

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**Blood Platelets in Splenic Anemia, with Special Reference to Treatment by Splenectomy.**—EVANS (*Lancet*, 1929, i, 277) presents an interesting paper on the blood platelets in anemia which is primarily of importance because of the correlation of platelet count with indication for operation. He notes, first, that the hemorrhagic tendency in splenic anemia may be due either to a mechanical factor, probably related to venous stasis associated with splenic and portal thrombophlebitis, or with a thrombopenia. He states that thrombosis of splenic veins and portal veins is of frequent occurrence and that thrombosis both in the portal system and the peripheral system may occur as a postoperative complication, occasioning at times a gross and persistent increase in the platelets after removal of the spleen. The patients that show a thrombotic tendency have normal or elevated platelet counts before splenectomy. These patients are operated upon with considerable risk because of the possibility of thrombosis, which may be fatal. It is possible, on the other hand, to recommend splenectomy with the greatest amount of confidence in those cases in which there is a thrombopenia. The article then gives a word of warning which should be of importance to medical men and to the patient: operate on the thrombocytopenic group, but keep away from operative procedures in the thrombocythemmic group.

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**A Study of the Nature of the Urea Concentration Test and its Value as a Test of Renal Function.**—There have been innumerable types of tests advocated for the determination of the functional efficiency of the kidney. Some of these, and often these more complicated tests give the most information, have been discarded because of technical difficulties which prevent their general use in the study of any considerable number of patients suffering from nephritis. Others have not stood up, when extensively used, to even a fair degree of accuracy. The two functional kidney tests most widely used in this country at the present

time include the well-known phenolsulphonephthalein test of Rowntree and Geraghty, which is entirely an estimation of the kidney function at the time the examination is done, and some one or another modification of the dilution-concentration ability of the kidney. The urea concentration test appears to be quite generally employed in England since its introduction by McLean and De Wesselow in 1920. WINTROBE (*J. Lab. and Clin. Med.*, 1929, 14, 848) writes that this particular functional test is of theoretic value because it is simple and it represents the test of a function normal to the kidney. He shows in his studies that it is relatively accurate. Substantiation of this latter statement is found in the study of forty-nine healthy students whose kidney function was contrasted, after the usual laboratory examinations which excluded gross nephritis, by two methods, phthalein elimination and urea concentration. They both indicated that the kidney was healthy but the urea test seems to be a very imperfect quantitative indicator of the function of the kidney because of the variations in concentration of urea which occur possibly as a result of, but depending upon, alterations in the amount of urine excreted. In the series of fifty-six patients who were believed to have nephritis on clinical findings, the urea-concentration test proved definitely superior to the phthalein where there was passive congestion from cardiac failure.

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**Variability of the Tubercle Bacillus.**—The wave of enthusiasm that has swept over France and some other European countries, following the announcement of Calmette that he has been able to vaccinate babies against tuberculosis by feeding them attenuated living preparations of the tubercle bacillus, has not been received in this country with more than a certain healthy skepticism. Indeed, many objections have actually been advanced on theoretic grounds, despite the ever-increasing thousands of children in Europe who have been treated without harm up to the present at least. What the future will bring out is another question. PETROFF (*New England J. Med.*, 1929, 200, 1148) at a recent meeting of the Massachusetts Tuberculosis League explained why he considered the method unsafe and told how the *Bacillus Calmette-Guerin* (B. C. G.) had been elaborated. Briefly, the development of this apparently harmless strain of tubercle bacilli depends upon the principle of microbic dissociation, "the process of variation in the offspring from the mother colony. Upon cultivation, this variation can be demonstrated first by cultural characteristics . . . upon subsequent cultivation there will be many variants from the mother colony. The two, or, perhaps, three, variants may differ from each other not only in colony structure, but also in tinctorial characteristics, virulence and other biologic characteristics." In Petroff's experimental work he was able to develop from a common mother colony two distinct dissociated strains, R colony and S colony, the former avirulent, the latter virulent for guinea pigs. This research explains B. C. G.; but, and a very big but, the R strains may be mutated into the S cells by certain procedures, such as cultivation in media containing 5 to 10 per cent homologous antiserum and the R strains are apparently not entirely free from some organism of S strain, no matter how carefully cultivated. These last two observations most assuredly present experimental evidence indicating possible dangers of feeding B. C. G. to children.

## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

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**Complications and Mortality of Appendicitis.**—WARREN (*Lancet*, 1929, ii, 16) writes that appendicitis appears to be developing a more severe character or is more common. The disease shows a considerable variation in its severity, depending on time and place. The mortality in the author's experience varies from 3 to 10 per cent. Expectant treatment may give good results in certain hands, but as a general measure its advantages are not proved, and its wide adoption might lead to further disasters. The mortality is greatest in children who are certainly not cases for expectant treatment, owing to the rapid and insidious way in which complications, such as peritonitis, develop in young subjects and their liability to acidosis from starvation. Early diagnosis and immediate operation are the counsels of perfection, but failure to diagnose early is by no means always the fault of the practitioner, for in children and old people the diagnosis may be quite difficult and many people regard a stomach ache too lightly. The main causes of death are peritonitis and mechanical obstruction. The latter can be very largely prevented by suitable technique at operation, and a careful watch should be kept in this important complication.

**Surgery of the Esophagus.**—SAINT (*Arch. Surg.*, 1929, 19, 53) states that the problems which have rendered surgical procedures in this sphere so difficult, and which still remain to be overcome, have been discussed. They lie in the anatomic structure and relationship of the esophagus and in the risk of fatal infection of the pleura and the cellular tissue of the neck and mediastinum. The numerous operations devised and performed for the extirpation of esophageal carcinoma have resulted in an appalling mortality. It is pointed out that such tumors are highly malignant, that they metastasize readily and that by the time they give rise to symptoms they usually have spread beyond the limits of surgical removal. The various methods used for the plastic formation of a new esophagus in cases of benign cicatricial stricture believed to be impermeable are described. There is a mortality of 20 per cent in the cases reported in the literature. This reason makes plastic operations undesirable procedures, to be avoided by early and adequate dilatation and by impressing on the patient the necessity for further dilatation at stated intervals. It would seem too that plastic operations have been undertaken unjustifiably, in many cases, the inability to pass the smallest sound being taken as the indication of impermeability. In nearly all such cases, however, a swallowed silk thread can worm its way through the stricture and then be used as a guide for sounds.

**The Use and Abuse of Iodized Oil in the Diagnosis of Lesions of the Spinal Cord.**—CRAIG (*Surg., Gynec. and Obst.*, 1929, 49, 17) says that iodized oil injected into the subarachnoid space is an invaluable adjunct in the armamentarium of the neurologist and the neurologic surgeon in diagnosing compression of the spinal cord, but it has its use and abuse. This diagnostic procedure should always be employed in conjunction with a complete examination, and the results obtained should never occupy more than relative importance in the establishment of a diagnosis. The irritative action on the meninges contraindicates its use in frank inflammatory lesions. By the use of iodized oil, the presence of tumor of the spinal cord can be detected earlier in certain cases, and the fact that there is a response to jugular pressure does not preclude its use. The outstanding use of lipiodol is for the confirmation of a suspected tumor of the spinal cord, and its greatest abuse is its employment in cases in which a complete examination would have established a diagnosis.

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**Hypernephroma.**—JUDD and HAND (*J. Urol.*, 1929, 22, 10) claim that carcinomas of the renal cortex are extremely malignant and are often well advanced before they produce symptoms. Alveolar carcinomas, in which but little attempt at cellular differentiation is made, are the most highly malignant of the various types of renal carcinoma, whereas adenocarcinomas are less malignant as judged from their clinical course. It is necessary that all of these malignant tumors should be submitted to gradation on the basis of cellular differentiation before it will be possible to arrive at more exact knowledge of the effect of treatment and the prognosis in the individual case. Not all of these deaths were due to the malignant condition. Many of these patients have lived for several years and then died from other causes. Some were known to have metastasis at the time they were operated upon and from the evidence at hand it would seem that the condition was arrested for a time. Therefore, even in these cases nephrectomy could seem to offer a reasonable degree of palliation. From the fact that 106 of their patients lived from three to twenty-two years, the authors believe that they are justified in the opinion that surgery will cure a definite proportion of them.

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**Pyelography and Cholecystography.**—EISENDRATH and AREUS (*Surg., Gynec. and Obst.*, 1929, 49, 1) say that the older criteria, as emphasized by Cole, in 1917, which were employed to differentiate the shadows of biliary and renal calculi are of little value at the present time. One can exclude from consideration the coral-like or branching renal calculus. The anatomic juxtaposition of the gall bladder and kidney in normal persons makes it possible to confuse shadows of biliary with those of renal calculi. The radiographic opacity of any calculus is not only dependent upon the atomic weight of the constituents, but to the structure and thickness of the calculus. Soft calculi are much less opaque than hard calculi. The form and opacity of biliary and renal calculi have many points of resemblance, so that these two criteria alone cannot be considered pathognomonic. The range of mobility of biliary calculi, is as a rule, greater than that of renal or ureteral calculi. If, however, the latter have formed in a dilated renal pelvis or ureter,

or both, a wide range of migration is possible. Cholecystography or pycelography or these two methods combined are very valuable additions to our diagnostic resources in the differentiation of biliary and renal calculi. Multiple exposure should be made by rotating the patients, because in some positions the suspected calculus may appear in the gall bladder or the kidney, while in others its true position is at once evident.

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**Impression Resulting from Three Thousand Transfusions of Unmodified Blood.**—BLAIN (*Ann. Surg.*, 1929, 89, 917) claims that favorable results obtained from 3000 transfusions have stimulated enthusiasm regarding transfusions and have made the clinic determined to extend the treatment not only to frank anemias, but to complicated surgical cases and bad surgical risks. Even moderate anemia before operation means prolonged and stormy convalescence after operation. Severe hemorrhage produces a deficiency of valuable blood constituents other than corpuscles and iron. Chronic secondary anemia without apparent cause, or persisting after the cause is removed, constitutes the basis of many cases of poor "health" and "chronic invalidism." A simple method whereby unmodified blood can be rapidly transferred from donor to recipient should be employed, and exposure of the blood to the air should be avoided. Universal donors may be used safely. A transfusion properly given presents practically no contraindications and produces essentially no reactions.

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## THERAPEUTICS

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UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,  
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,  
BOSTON, MASS.

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**The Rectal Administration of Liver in Pernicious Anemia.**—In view of the occasional almost total inability of certain patients with pernicious anemia to eat adequate amounts of liver in any form whatsoever, and at times even to take orally any of the liver extracts, HANS PULFER (*Deutsch med. Wchnschr.*, 1929, 55, 99) tried the rectal administration of liver in 2 cases with results quite as satisfactory as those usually obtained with its oral administration. The liver, finely ground, thinned with milk and then passed through an exceedingly fine sieve, was prepared for rectal administration by the addition of 15 drops of tincture of opium. This thin mixture was then injected slowly into the rectum which had previously been prepared with a low cleansing enema. A

daily dose of 150 grams of liver was thus administered. In order to increase the effectiveness of this mode of administering liver hepatopson, a liver extract was frequently added to the prepared liver. No difficulty was observed in having these enemas retained and their absorption seemed to be rapid and complete.

**The Surgical Treatment of Angina Pectoris Based on Researches upon Man.**—As a result of his prolonged investigations concerning the mechanism of angina pectoris, along with consideration of the investigations of others, DANIELOPOLU (*Weiner klin. Wchnschr.*, 1929, 42, 67) supports his previous conclusions that one of the most important influences responsible for the attacks is that of a pressor reflex. He further points out the very high mortality of the Jonnesco operation and the serious and lasting after effects of many modifications of this operation in which either the inferior cervical ganglion, the stellate ganglion or both are resected. The author finds it possible to avoid these dangers and at the same time to obtain equally effective relief of the attacks by a much simpler procedure. He advocates the removal of the superior cervical ganglion on the left side, leaving intact the inferior ganglion and the stellate ganglion. The connecting branches, however, which lead out of the inferior cervical ganglion as well as those which pass to the sixth, seventh and eighth cervical and first dorsal segments are sectioned. In addition, the vertical branches of the vagus in the neck are cut and the vertical nerve is also severed. This procedure not only diminishes the pain or prevents its occurrence but is also associated with an appreciable and lasting diminution in the blood pressure. It has been performed in approximately 25 patients with the foregoing results and so far has proved entirely free from danger.

**Endonasal Administration of Insulin.**—Seeking a method of administering insulin other than by hypodermic injection, WASSERMEYER and SCHAFER (*Klin. Wchnschr.*, 1929, 8, 210) experimented with its application intranasally. They employed a powdered insulin which was mixed with pure borax. In tests on normal subjects they found a noticeable reduction in blood sugar two hours after the administration of 17 units and a somewhat less marked reduction with smaller doses. Similiar results were obtained in a small group of well-controlled diabetic patients as illustrated by the fact that the fasting blood sugar was reduced from 183 to 74 mg. within two and a half hours after a dose of 13 units. Equally satisfactory results were obtained in others. Further investigations on less well-controlled ambulant patients confirm the fact that insulin is well absorbed following intranasal administration. The one question not yet settled by their investigation is that of whether or not the dose by this mode of administration is susceptible of sufficiently precise control.

**Vitamin A as an Anti-infective Agent.**—MELLANBY and GREEN (*Brit. Med. J.*, 1929, i, 984), in a preliminary communication call attention to the effect of vitamin A in raising the resistance of the body to bacterial infection. They observed that animals deprived of vitamin A died ultimately with multiple foci of infection, whereas control animals receiving vitamin A remained in good health. Animals which had

developed infective lesions, if given in time abundant vitamin A, usually recovered completely. On the basis of this observation, the authors undertook to investigate the effect of two preparations rich in vitamin A ("radiostoleum" and preparation Y) on puerperal septicemia. Of the 24 cases not receiving the vitamin A, 22 died; in the 5 cases receiving vitamin A there was no death, and all made complete recovery. It would appear that the effect of vitamin A is rather to increase gradually the general resistance than to act as a substance having a specific bactericidal or antitoxic effect. In all the 5 cases reported *Streptococcus hemolyticus* was cultured from the blood stream. There is reason to believe that the anti-infective action of vitamin A is not a specific in puerperal septicemia, and it is most probable that the same increase in bodily resistance would be found in many other types of infection. The body in times of special stress, as in pregnancy, should receive an adequate and large supply of vitamin A in form of natural food. Such foods include egg yolk, green vegetables, milk, butter and cheese. Cod-liver oil also contains vitamin A in abundance.

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**The Clinical Use of Acetyldimethylodihydrothebain.**—The therapeutic effect of this derivative of thebain, commercially called "Acedicon," was tested on 1200 patients by BERTRAM and STOLTENBERG (*Klin. Wchschr.*, 1929, 8, 883). The drug was administered orally in doses of 0.005 to 0.01 gm., up to 0.01 to 0.03 gm. daily. The subcutaneously administered dose was 0.005 to 0.01 gm. The effect of the drug was identical whether administered by mouth or subcutaneously. In patients with pain the effect was less intense and of shorter duration than that of morphin. The authors do not feel, however, that this aspect of the problem is settled. In pathologic states associated with cough the drug exerted beneficial effect. In suppressing cough due to tracheitis and acute bronchitis, 0.01 gm. "acedicon" had a better effect than 0.03 gm. codein. In patients with pneumonia, and severe hiccough, the drug had no advantage over a number of other therapeutic agents. It was used successfully in cases with bronchiectasis and pulmonary congestion due to cardiac failure. In a number of patients, especially after larger doses, 0.01 gm., a soporific effect was noted. Depression of the respiration was not observed. In patients with dyspnea the air hunger was reduced. No untoward effect on the cardiovascular system was observed in normal subjects, or patients with cardiovascular diseases. Similarly, changes were not observed in the metabolism and body temperature. In 18 patients vomiting lasting for several hours occurred. Associated with this ataxia and signs of collapse developed. The authors advise to begin always with smaller doses (0.005 gm.). When the drug was used continuously the analgesic and soporific effect disappeared within a short time. The effect on cough lasted longer. There were patients with cough, however, who failed to respond after a prolonged use of the drug. Withdrawal symptoms were not observed with certainty. The problem of whether or not acetyldimethylodihydrothebain is a habit-forming drug cannot be considered as settled. In three morphin addicts "acedicon" proved to be a successful substituting agent. The authors believe that the effect of this drug is between that of morphin and codein, and closer to codein than to morphin.

## PEDIATRICS

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UNDER THE CHARGE OF

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**Enuresis in Children.**—MOHR and WATERHOUSE (*Am. J. Dis. Child.*, 1929, 37, 1135) studied 15 children suffering with enuresis in a home, to determine the causes of enuresis, the response to a routine treatment, and the physical and mental differences between this group and a group of 15 normal children in the same home. They found that familial enuresis was common, several children in a family suffering with the disease, and the parents of some giving a history of enuresis also. The principal factors in the production of enuresis in these children seem to be poor training, emotional factors, physical factors, suggestion and fatigue. Enuresis in this group was frequently the result of poor training, many of the children had never learned the dry habit. Two cases were noted in which the control of the bladder had been acquired but with subsequent onset of enuresis. Physical comparison of the enuretic and control groups indicated that there was no relationship between specific physical defect and enuresis. The children with enuresis were relatively in poorer nutritional condition and of slightly inferior general physique. The children with enuresis had less efficient cardiovascular systems as measured by a cardiovascular efficiency test. Physical differences between the children with enuresis and normal children may be of the nature of constitutional variations. In this group the studies did not confirm the reports of other groups of a reversal of the normal relationship between concentration of urine voided during the day and that voided during the night. These enuretic children were emotionally less stable and betrayed a greater number of emotionally conflicting situations than did the normal group. The variety and combinations of causative factors ranging from purely organic to purely psychogenic were in keeping with the view that enuresis is frequently a symptom of neurosis. The therapeutic procedure was largely a limiting of fluid intake after 5 P.M.; sleeping on the floor without mattresses, on a rubber sheet; the cleansing of the sheets by the children themselves; the encouragement of the children by praising the dry nights. This resulted in complete relief in 4 cases and improvement in 7 others.

**Cervicovaginitis.**—STEIN, LEVENTHAL and SERAD (*Am. J. Dis. Child.*, 1929, 37, 1203) recommend the use of the vaginoscope for the careful study and treatment of young girls with genital inflammation. Cervical involvement is an essential part of the underlying pathologic process in cases of so-called vulvovaginitis. This fact is appreciated after vaginoscopic study. The urethra also is frequently involved. Because of this fact, the authors recommend the term cervicovaginitis instead of vulvovaginitis. It was necessary to treat directly the cervix and the urethra in order to insure absolute cure. They found that about



one-fifth of their cases were of gonorrheal origin and they found that treatment with mercurochrome ointment was a simple and effective method. In all varieties of cervicovaginitis the duration of treatment with 1 per cent mercurochrome ointment in the patients with gonorrheal infection was eleven weeks, while those in whom infection was suspected and those in whom it was nongonorrheal were cured in less than one-half the time. There were recurrences of discharge after three months in about 20 per cent of the patients with gonorrheal infection, while there was no recurrence in those in whom the infection was nongonorrheal. A long period of observation using the vaginoscope after the cessation of the active treatment was required in order to determine the cure.

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**The Clinical Value of Sunlight Through Ultraviolet-transmitting Glass.**—CALDWELL and DENNETT (*J. Am. Med. Assn.*, 1929, 92, 2088) found that infants and children may be given sun baths of two or three hours daily throughout the winter, not as a substitute for ultraviolet-lamp irradiation for the cure of disease, but as a prophylactic measure. They found that there were ample ultraviolet rays in the antirachitic range in this latitude during the winter to be of definite value to those receiving them through a special type of window glass when exposures are made in the direct path of the sun's rays, since enough of these rays penetrate the glass to prevent rickets and spasmophilia in a normal properly fed baby. They also point out that the general impression that ageing of the glass decreases the therapeutic effect is erroneous.

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**Respiratory Disorders in Infants.**—ABRAMSON and BARONBERG (*J. Am. Med. Assn.*, 1929, 92, 2156) in this study attempted to lessen the incidence of these infections by putting into practice the principles of aseptic nursing. During the course of a winter all persons coming in contact with the infants in one ward were required to wear surgical masks and to scrub their hands thoroughly before the examination or handling of children. A comparison made with infants in a control ward where no such precautions were taken, showed that a decrease of respiratory diseases of only 10 per cent was accomplished by this means. The greatest difficulties arose from occasional infractions of technique on the part of the nurses as well as from the impossibility of preventing contact infections from child to child. Infants who were kept in cribs showed almost a 50 per cent higher incidence of respiratory disorders than those cared for in bassinets. The frequency of infection per child was less in the protected than in the control ward. They also found that aseptic nursing was of no value in preventing the spread of an outbreak of varicella.

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**The Care of Rheumatic Children.**—FORDYCE (*Brit. Med. J.*, 1929, i, 146) observed 540 children in a special outpatient clinic for rheumatic children. Of these, 321 had apparently no permanent cardiac lesion, while 119 had established cardiac lesions but with satisfactory myocardial responses. There were 25 cases in which there was uncertainty

as to whether the cardiac injury was permanent or not. Cardiac lesions and failing heart were noted in 41 cases and 9 had acute rheumatic fever, 16 had congenital heart deficiency. There were 9 deaths from rheumatic carditis. Exclusive of cases of congenital heart disease and all cases of acute rheumatic fever, the outcome of which hung in the balance, and giving the benefit of the doubt in prognosis to all cases of doubtfully permanent cardiac lesion of 515 cases recommended to the clinic as rheumatic and accepted as such, 346 could be regarded as suffering from no permanent heart lesion, while 119 had permanent lesions, but showed good response and 41 showed evidence of failing heart muscle and 9 died. In other words, 50 children, or 10 per cent, had died or were unlikely to survive childhood, and 119, or 25 per cent, were permanently crippled to a greater or less extent. In the active care of the children the removal of infected tonsils was greatly stressed. Of the 531 rheumatic children, 130 underwent tonsillectomy in a hospital and 22 at a school clinic. Four cases were refused permission for operation by the parents and in 67 other cases operation was greatly needed. Thus, in 213 out of 531 children, or about 40 per cent, tonsillectomy was considered advisable. In none of the patients operated upon did unfavorable symptoms develop from the operation, regardless of how active the rheumatic symptoms were at the time.

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**Familial Purpura Hemorrhagica Without Thrombopenia.**—ROTHMAN and NIXON (*J. Am. Med. Assn.*, 1929, 93, 15) made a critical analysis of cases reported in the literature and comment that proper classification is extremely difficult. These cases did not correspond to any other well-known types of purpura. The purpuric manifestations associated with a normal platelet count and the heredofamilial factor of fairly constant observation, where such a considerable variation exists in the coagulation and bleeding times as well as in the clot-retraction phenomenon, the confusion is partly due to the lack of uniform laboratory methods for these determinations and also to the fact that a definite variation occurred in many of the individual cases at subsequent examinations. This condition must carefully be differentiated from other forms of purpura, especially from the rare case of familial Werlhof's disease and also from hemophilia and familial telangiectasia. The etiologic mechanism in this form of purpura is not clearly understood, but it has been attributed to a functional insufficiency of the platelet. The inability of the clot to retract may be due to the absence of the ferment retractozyme, or its presence in a less active form. Too much emphasis should not be placed on the ability of the clot to retract, as this phenomenon is not always constant in normal individuals. In some cases abnormalities in the size of the platelets and alterations in the protoplasms and granules have been found. Pyknosis and other evidences of degeneration are frequently met. Little can be said concerning the treatment employed. Blood transfusion has proved of great aid in tiding the patient over the severe attacks of bleeding. Roentgen ray irradiation of the liver and spleen is of doubtful value. In patients bleeding from the nose, the hemorrhage was diminished by cauterization or removal of tonsillar tissue. As regards removal of the spleen, the value of this is not settled at the present time.

**The Clinical Significance of the Water of Metabolism in Children.**—GOLDSTEIN (*Arch. Ped.*, 1929, 46, 371) states that the water of metabolism is a very important factor and is of great clinical significance in children in health and in diseased conditions. Diet modifies water balance to a great extent. Carbohydrates and proteins favor water retention but in excess, especially if the protein is over 20 per cent of the total calories. Metabolism and water loss is stimulated with a subsequent loss in weight. If carbohydrates are less than 3.5 per cent in the diet, acidosis may result. A high-fat diet encourages water loss and, indirectly, weight loss. In severe cases of vomiting with great loss of water and hydrochloric acid there may develop a retention of alkalis and an alkalosis. There is no question but that marked changes in the water balance cause the same influence to partly change the alkaline reserve. Fortunately, the latter content of the plasma is easily compensated and is, therefore, more or less constant.

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## GYNECOLOGY AND OBSTETRICS

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UNDER THE CHARGE OF

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**Surgical Treatment of Uterine Prolapse.**—The number of operative procedures which have been recommended for the surgical cure of uterine prolapse is so large that it is often difficult to decide which procedure should be employed. Of course, the real gynecologist will vary his procedure to meet the conditions present in the individual case. The preferences at the Mayo Clinic have been detailed by MASSON (*Minn. Med.*, 1929, 12, 67), who states that during the child-bearing period, repair of lacerations and shortening of the round ligaments should be performed. External shortening of the round ligaments of the Alexander type is now seldom advised. Opening the abdomen adds little if any risk to the operation and often other surgical conditions within the abdomen can be attended at the same time. He prefers the modified Gilliam type of operation, shortening the round ligaments through the internal ring, but he has also found the Baldy-Webster operation satisfactory. If a raw surface is to be left on the anterior uterine wall as the result of the separation of adhesions or myomectomy, the Coffey type of anterior plication of the round and broad ligaments is satisfactory. If a raw surface exists on the posterior surface of the uterus, posterior plication should be performed. If women are close to or have passed the menopause, and slight prolapse and troublesome cystocele or rectocele exist, he advises the Watkins

interposition operation, ligating the tubes if necessary and repairing the pelvic floor. In many cases, especially before the menopause, the uterus is too large for this procedure, and if the regular technique is followed the patients complain of a bulging in the introitus. To overcome this, it may be advisable to reduce the size of the uterus by removing part of it. A wedge-shaped piece can be removed from the fundus and the cervix can be amputated, but the author prefers to remove all of the anterior wall and thoroughly denude all the mucous membrane from the uterine cavity and cervix, cutting a wedge-shaped piece from the fundus on each side at the site of the entrance of the Fallopian tubes. Bleeding is controlled by suture and the resulting uterine tissue, less than half the size of the original organ, is sutured under the bladder in the regular way. This operation deserves special mention as it effectually cures the cystocele, eliminates the danger of carcinoma and prevents troublesome and dangerous sequelæ, such as distortion of the bladder base or anterior vaginal wall and the possibility of pregnancy. The Mayo operation for cystocele and prolapse is especially suited for the case in which a large cystocele and marked prolapse are present. In cases of marked prolapse with a relatively small cystocele, good results are obtained by performing perineorrhaphy and fixing the uterus to the anterior abdominal wall. In cases of extreme prolapse it is sometimes advisable to perform subtotal or total hysterectomy and anchor the vault of the vagina into the abdominal wound. It is sometimes advisable in elderly patients with a prolapse and large cystocele and rectocele to denude the mucous membrane on either side of the vagina from the introitus to the cervix and approximate these raw surfaces, leaving two narrow mucous tracts or canals to take care of any discharge from the uterus. If a vaginal hernia develops following a hysterectomy it is sometimes necessary to obliterate the vagina completely by first removing all the vaginal mucous membrane and closing the opening by multiple circular sutures, commencing at the top and working down to the introitus, simply leaving room for the urethra under the pubis.

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**New Technique for Lipiodol Injection of the Uterus.**—In the simplified technique which ADAIR and McDONALD (*Minn. Med.*, 1929, 12, 146) have developed for injecting lipiodol into the uterine cavity, the Rubin cannula is no longer used. Instead a rubber mushroom or retention catheter is inserted into the uterus by means of the regular mandrin used for the insertion of retention catheters. The anterior lip of the catheter is held with a tenaculum for convenience while placing the catheter but is released before the Roentgen ray exposure is made. The catheter is then drawn down so that the bulb or mushroom tip rests firmly over the internal os. Lipiodol is then injected and the plates made. In a few cases there has been a small reflux of lipiodol along the sides of the catheter into the vagina but this occurs only in the cases of multiparous women with more or less patulous cervixes and has been noted also in similar cases where the cannula has been employed. Aside from the simplicity of the method, the chief advantage is that instruments are not visualized in the hystrogram to interfere with the more accurate reading of the conditions represented in the picture.

**Conservative Treatment of Pelvic Endometriosis.**—According to WHARTON (*South. Med. J.*, 1929, 22, 267) every surgeon has to answer the following question when operating upon a case of pelvic endometriosis: Can I save the functions of menstruation and childbearing or is it necessary to remove the uterus, tubes and ovaries? His answer is that it is desirable to treat these cases conservatively in young women and when the conservative treatment is successful, the end result is well worth while. In his experience, such patients have conceived and for periods of six years have remained in perfect health. If one can be reasonably sure that the ovaries can be stripped completely of endometrial growths, if the uterus can be left in a healthy state and if the pelvic organs can be left in normal positions, then one can attempt conservatism with a fair chance of a gratifying result. In his experience, in patients over thirty-five years of age, the pelvic disorders are so grave that conservatism is unwise. Also when both ovaries and the uterine wall are involved in endometriosis, conservative measures are very risky. This seems to us to be very sane advice and will undoubtedly be of help in reaching a decision when confronted with these interesting lesions.

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## OPHTHALMOLOGY

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UNDER THE CHARGE OF

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**Retinal Detachment Complicating Insulin Therapy (A Biophysicochemical Explanation).**—ALPERIN (*Am. J. Ophthalm.*, 1929, 12, 486) reports 1 case and has seen 2 others in which detachment of the retina appeared to be related to insulin therapy. The patient had suddenly gone blind in the right eye, with nothing unusual in the history but a vague, dull pain in the parietal region. The retina was hazy; there was no light perception. Diet was restricted and insulin withdrawn. The detachment of the retina gradually decreased and vision was recovered. In explanation, the author advances the theory of change in osmotic pressure causing changes in intraocular pressure. For any one of a number of reasons, hypoglycemia may occur in diabetic patients. The osmotic pressure is in direct proportion to the degree of ionization of the dissolved substances in the blood (electrolytes, such as mineral salts), and this is in direct proportion to the dilution of the electrolyte. Consequently, the thinner the solution, here the blood, the more molecules of the electrolyte will dissociate into ions and the greater the osmotic pressure in the hypoglycemic blood. Under such conditions it would be possible for fluid to pour into the eye through the congested ciliary vessels increasing intraocular pressure and producing the symptoms of acute glaucoma (Richter) or it could pass into the subretinal

space from the choroidal plexus, resulting in detached retina. The fundamental biophysicochemical changes are, in the author's mind, the same. The author recommends that the eye grounds of diabetic patients be examined from time to time, and if visual disturbances occur, that insulin be discontinued temporarily.

**Ocular Residua and Sequelæ of Epidemic Encephalitis.**—BARLOW (*Arch. Ophthalm.*, 1929, 1, 501) reports that ocular phenomena play an important rôle in epidemic encephalitis, appearing in the early stage, when they are usually transient and disappear in a few days or weeks, or in the postencephalitis or Parkinsonian stage. The third and sixth nerves are most frequently affected and occasionally the trochlear. The optic nerve is rarely involved; optic neuritis and papilledema are rather infrequent occurrences even in the early stages. The British Ministry of Health has stated that "In the diagnosis of lethargic encephalitis a negative sign of value in the absence of optic neuritis." Ophthalmoplegia is of frequent occurrence, appearing in two forms, peripheral and nuclear. The peripheral form always recovers; the nuclear may clear up if it is slight, but if more severe it always leaves some permanent paralysis. It may involve any part of the nuclear mass. Oculogyric crises occur most frequently, if not exclusively, in the Parkinsonian syndrome. Muskens has localized the lesion just in front of the posterior commissure, one of his reasons being that there is a frequent association of tonic lateral position of the eyes with the upward or downward position. The two bundles involved in these two forms of forced movement are close together only at one point—just in front of the posterior commissure. Nystagmus is frequently observed as a late symptom. It is of greatest diagnostic value when it is up or down, the lateral being present in numerous other diseases. Convergence paralysis is considered by many to be one of the most frequent eye symptoms in the Parkinsonian syndrome. This, however, requires differentiation between congenital and acquired convergence paresis. Paresis of accommodation, less frequently a complete paralysis, is one of the earliest eye symptoms and is frequently observed as a late complication. Formerly this was considered as a complication of diphtheria only. The pupil has proved of little value for it is extraordinarily inconstant. Argyll-Robertson pupil has been frequently observed in acute encephalitis, but is a rare occurrence in chronic encephalitis. There is another symptom of the eyes in the postencephalitic Parkinsonian stage in which the eyeballs are peculiarly rigid, but in which there is no paralysis of the eye muscles. The eyes can be moved with effort if the patient be aroused. Cords has designated it "myostatic rigidity of the eyes." The face has a masklike expression, the action of the facial muscles is entirely abolished and the eyes are expressionless, staring into space for hours at a time.

**Investigations on the Toxic Action of Trichlorethylene, Particularly on the Eye.**—MEYER (*Linn. Monatsbl. f. Augenh.*, 1929, 82, 309) reports that various injuries to the eye, such as a black fleck on the fovea centralis, absence of the corneal reflex, insensitivity of the cornea, absence of the secretion of tears, irritation and swelling of the conjunctiva, double vision, swelling of the ocular fundus, dyschromatopsia,

retrobulbar neuritis have been reported from industries and professions as due to trichlorethylene. Unfortunately, in most of the cases an adequate physical examination had not been made and in many of the cases the possibility of the concomitant action of other toxins, such as alcohol, could not be excluded. It is also possible that decomposition products of trichlorethylene may have caused the damage, since it decomposes in contact with metals, particularly iron. Late injury to the eye had never been reported. The author, in his experimental investigations, used 5 dogs, anesthetizing 2 repeatedly, giving the trichlorethylene subcutaneously in the other 3. Under deep anesthesia the corneal reflex was absent and the pupils were usually medium in width and always reactionless. In no case was there a change in the ocular fundi. Subcutaneous injection began with 1 cc. and increased at the rate of 2 to 3 cc., until the 3 animals had received 45 cc., 56 cc. and 30 cc. respectively. At autopsy, no changes were found in the retina and histologic examination of the optic nerve, carried to beyond the chiasma, was entirely negative. Further investigations on apes, in the author's opinion, might be advisable since Roemer has shown that reactions of the optic nerve of certain species are not the same as in man.

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF  
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**The Physiology of Vestibular Nystagmus.**—Vestibular nystagmus is an intricate physiologic phenomenon, which is important as an aid in neurologic and otologic diagnosis, and as a test of fitness in aviation. In outlining the present status of the knowledge of the physiology of vestibular nystagmus, IVY (*Arch. Otolaryngol.*, 1929, 9, 123) summarizes as follows: "On stimulation of the nonacoustic labyrinth, movements of the eyes occur which are compensatory in nature. The movement of the eye is characterized by a slow movement called the deviation, or slow component, and a quick movement opposite in direction to the deviation called the nystagmus, or quick component. The deviation of the eyes is due entirely to stimulation of the labyrinth. The nystagmus is most probably due to a reflex *via* the muscle centers of the eyes which is excited by the stimulation of kinesthetic sensory nerve endings in the muscles of the eyes, and is not due to a cerebral reflex arc. The cerebrum exercises its well-known inhibitory control over this reflex. It is pointed out that the cristæ of the canals are most probably not stimulated by the inertia effect of canal currents, and that Maxwell's theory, which holds that the cristæ of the ampullæ are stimulated by changes in tension of the utricular membrane caused by inertia effects

in the larger bodies of fluid in the vestibule and utricle, is more reasonable and probable. It is shown that a correlation exists between the type of nystagmus that results from rotation in the various visual planes in the dog-fish and in man."

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**The Clinical Significance of Spontaneous Nystagmus.**—Because its anatomic basis is best known, spontaneous nystagmus is the most important symptom produced by the labyrinth. Inasmuch as it can be produced by various organs, the clinical evaluation of spontaneous nystagmus is often difficult. Otologically, spontaneous nystagmus can be divided into a labyrinthine, and a nonlabyrinthine, type, although the pathogenesis of nonlabyrinthine nystagmus is obscure in many respects, so that diagnostic conclusions based on this type of nystagmus are as yet hardly possible. In order to differentiate between labyrinthine and nonlabyrinthine nystagmus, BRUNNER (*Arch. Otolaryngol.*, 1929, 9, 1) utilizes the following points: (1) *Dizziness*—labyrinthine nystagmus is always accompanied by labyrinthine dizziness (turning dizziness, tactile dizziness); (2) *Association of Eye Movements*—spontaneous labyrinthine nystagmus always exhibits associated eye movements; (3) *Form of Nystagmus*—spontaneous labyrinthine nystagmus, in its typical form, is combined horizontal and rotatory, or only rotatory. Diagonal spontaneous nystagmus is practically always, and vertical spontaneous nystagmus is often, of nonlabyrinthine origin; (4) *Inversion of Experimental Optical Nystagmus*—as elicited by means of the author's revolving umbrella. Normally, and in persons with spontaneous labyrinthine nystagmus, the "umbrella test" causes a coarse horizontal nystagmus in the direction opposite to that in which the umbrella is turned, whereas in those with spontaneous nonlabyrinthine nystagmus several abnormal reactions may occur, which can be grouped under the term "inversion of experimental optical nystagmus." In order to render this "inversion" clearer, Brunner cites 10 illustrative cases, giving the findings of the various functional tests of the labyrinth.

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**A Comparison of the Outlines of the Frontal Sinus in Vivo as Shown by Transillumination and the Roentgen Rays.**—By indicating with opaque paint on the skin the apparent contour of the frontal sinuses in a small group of medical students, as revealed by transillumination, and then taking radiographic films of the same sinuses, FETTEROLF and SPRENKEL (*Arch. Otolaryngol.*, 1929, 9, 181) found that the frontal sinuses were decidedly smaller than they appeared to be on transillumination, the Roentgen ray films showing their upper margins to be from  $\frac{1}{2}$  to  $\frac{3}{4}$  inch lower than the impression conveyed by transmitted light.

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**"A Working Hypothesis for Research in Otosclerosis."**—YATES (*Ibid.*, p. 852) reasoning from results of his clinical and audiographic investigations, believes that clinical otosclerosis is at times the terminal stage of subacute otitis media in which the products of inflammation of the middle ear are carried away by the Eustachian tube.



## RADIOLOGY

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UNDER THE CHARGE OF

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**Acute Massive Collapse (Atelectasis) of the Lung.**—Acute massive collapse (atelectasis) of the lung, states BOWEN (*Am. J. Roent. and Rad. Ther.*, 1929, 21, 101) is a definite clinical entity characterized by more or less airlessness of a lobule, part or all of a lobe, a whole lung or even of both lungs. Although described with surprisingly few errors more than seventy-five years ago, it has in recent years been rediscovered as a post-operative complication. It is rarely seen without some measure of increased or retained secretion which may be excessive and which rapidly becomes purulent. The most important premonitory symptom is a moderate elevation of temperature; the most notable subjective sign is dyspnea, and the most reliable physical and Roentgen finding is displacement of the heart toward the affected lung.

Much of the discussion as to its etiology is still on a theoretical basis. It has been attributed to paralysis of the diaphragm or a part of it, to fixation of the diaphragm by pleuritis or traumatism to the upper abdomen, to reflex action from injury of the vagus, and to plugging of a bronchus with mucus. Bowen inclines strongly to the theory of plugging by mucus. He also regards the pre-anesthetic administration of morphin and atropin as a predisposing factor, and he thinks that general anesthesia cannot be absolved from all suspicion as an etiologic factor. Patients experiencing the so-called "wet anesthesia" should be watched with especial care during the early postoperative period in order that no premonitory sign of collapse shall be missed.

The condition may be massive, involving a lobe or lung, or partial, lobular or patchy. Accordingly attacks may be fulminant, moderate, latent or evanescent. In by far the greater number of cases a rise in temperature is the first symptom of impending collapse. It rarely exceeds 102° F. Any rise of temperature after the postoperative reaction is over should suggest the thought of atelectasis. In the fulminant type the face is suffused and the expression anxious; dyspnea is urgent and there is marked diaphoresis; the patient complains of a sense of tightness amounting to real intrathoracic pain. Commonly a sense of equilibrium is established within a few hours and the course is thereafter less urgent. In severe cases, on inspection, it may be noted that the patient does not lie straight in bed but the affected side of the thorax is contracted and fixed, and the shoulder is depressed toward the hip. Auscultatory signs vary from an entire absence of breath sounds over a wholly collapsed lung, to many râles in adjacent unaffected portions of

the lung. The heart is displaced toward the affected side in ratio to the extent of atelectasis.

In the roentgenogram the density of the affected area is marked and fully as great as that seen in lobar pneumonia; and lobar or broncho-pneumonia is likely to enter into the differential diagnosis. Due regard for the other signs, particularly cardiac displacement, should make the diagnosis clear.

The duration of the condition varies from a few hours to four weeks. There are no specific remedies and the use of drugs, if any, must be on the expectant plan. Sante has noted spontaneous reinflation when the patient was rolled back and forth on the uninvolved side; Gairdner, seventy-five years earlier, reported a case of collapse which disappeared under an emetic and forced decubitus on the opposite side. Bowen admits the merits of Sante's procedure but doubts that it will prove a panacea for all cases. Bronchoscopic drainage now has 14 successes to its credit, with no actual failures, and the outlook for this method is promising.

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**Nature of Arthritis.**—A fifth of all cases of arthritis, especially those which are atrophic in type, show a slight decrease in metabolism, according to PEMBERTON (*Radiology*, 1929, 12, 235). Metabolism of nitrogen, fats, calcium, phosphorus and uric acid seems normal, but there is a delayed removal of ingested glucose from the blood which closely parallels arthritis and focal infection. Coincident with this there is a delay in the utilization of oxygen, at least in the smaller vessels, due to a vasoconstriction, or a similar change, inducing a sort of anemia in certain structures. A study of the capillaries of the arthritic by Lombard's method of direct microscopic observation, shows that they contain on the whole less blood than normal, and that the stream tends to be sluggish and interrupted. These phenomena help to explain the beneficial effects of physiotherapeutic measures, notably exercise, massage and heat, all of which are widely used by the laity. Both exercise and external heat increase the circulatory rate, as shown by a sharp rise in the oxygen percentage saturation of the peripheral blood; they also induce an increase in the red cell count. The influence of massage in increasing the circulation is not so evident, but it does, nevertheless, have a very marked effect on the red cell count.

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**Rôle of the Roentgen Ray in Determining the Resectability of Gastric Cancer.**—Underlying all factors affecting resectability, in the opinion of MOORE (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 226), are three of basic importance, namely, the situation of the gastric cancer, the presence or absence of fixation to adjacent structures, and the presence or absence of metastasis. By demonstrating the seat and extent of the growth the Roentgen ray renders its greatest service. Cancers in the cardiac third of the stomach are seldom accessible for resection, while those in the pyloric third are readily resectable so far as situation alone is concerned. In general, cancers confined to the lower half of the stomach, *i. e.*, distal to the incisura angularis, can be excised, but those which involve the upper half are not resectable. If the cancer is of the scirrhus, infiltrating type, an allowance of 2 or 3 cm. beyond the invasion shown in the roentgenogram should be made. When attachment

to the pancreas, mesocolon, liver, omentum, colon or abdominal wall is firm, resection is likely to be impossible. If fixation is not obvious, it is always to be surmised when a cancer is extensive or when the palpable tumor greatly exceeds the defect in the gastric shadow. Concerning metastasis the Roentgen ray yields scant information. Metastasis to the lungs or bones is readily demonstrable, but occurs very rarely from cancer of the stomach. Metastasis to the liver and abdominal lymphatics is common, is not discoverable with the Roentgen ray, and often makes resection futile. On the whole, the interdict of the Roentgen ray against operation deserves and receives respect, while its assent to operation is merely conditional and subject to unavoidable error.

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**Treatment of Carcinoma of the Rectum.**—Sixty-five cases of carcinoma of the rectum are reported by JONES (*Am. J. Roent. and Rad. Ther.*, 1929, 21, 168) in which treatment was by Roentgen and radium irradiation. In 10, or 15 per cent of the total number, the patients are well, having remained so for periods varying from three to seven years. Although the treatment of choice for an operable cancer of the rectum is operation by the combined abdominoperineal routes, if operation is refused or the condition is inoperable there is sufficient evidence that a cure can be obtained in certain cases and marked palliation in others by the combined use of radium and Roentgen rays.

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**Massive Hemorrhage from the Gastrointestinal Tract.**—SANTE (*Am. J. Roent. and Rad.*, 1929, 21, 144) reports 2 cases of severe hemorrhage from the gastrointestinal tract in which no ulcer, cancer or other organic cause could be found. Many cases of bleeding have been reported by others in which the point of bleeding could not be demonstrated. Explanation of the hemorrhage merely on the basis of seepage from engorged vessels has never seemed entirely satisfactory. Experimental work of Auer has suggested the possibility that the hemorrhage is a manifestation of autoreinoculation of a person previously sensitized by infection of the gall bladder, appendix or diverticulum of the intestinal tract with a resulting localized anaphylactic reaction. Sante reasons, therefore, that all patients having hemorrhages without any demonstrable organic lesion should be subjected to thorough examination for protein sensitization and for focal infection of organs which drain into the intestinal tract.

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**Technique of Gall-bladder Examinations.**—PILMORE (*Am. J. Roent. and Rad. Therap.*, 1928, 20, 539) has examined the gall bladder in 150 cases by making one film at full inspiration and another at complete expiration. He has found that at full inspiration the gall bladder usually moves downward and toward the midline of the body. At expiration the reverse occurs. The greatest movement is in tall thin persons and the least in stout individuals. Inspiration and expiration films frequently aid interpretation by shifting the gall bladder into a position where it is more readily visible, and by moving it away from areas of gas in the bowel.

# NEUROLOGY AND PSYCHIATRY

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**A Case of the Progressive Hypertrophic Polyneuritis of Dejerine and Sottas, with Pathologic Examination.**—DE BRUYNE and RUBY O. STERN (*Brain*, 1929, 52, 84) were able to find only 12 cases previously reported in the literature with histologic verification. Besides these they found 14 clinical records, 6 of which they consider as of doubtful value. These cases are summarized by the authors. They also review the discussions of the pathology and call attention to the fact that the essential lesions appear to be hypertrophy of the peripheral nerves, ganglia, and spinal roots, depending on 2 factors—one an increase in the interstitial tissue; the other, which is peculiar to the disease, a proliferation of the cells of the sheath of Schwann with a concomitant demyelination of nerve fibers. There is also an associated degeneration of the posterior columns of the spinal cord, the relation of which to the lesions in the nerves and the nerve roots may be consecutive, though this has not yet been definitely decided. They present a case examined by them clinically and pathologically. Gross examination at autopsy showed atrophy of the muscles of all four limbs, more noticeable distally than centrally. The peripheral nerves could be palpated, were somewhat larger than normal and excessively firm. The nerves were greater close to the ganglia and smaller peripherally. Nerves proximal to the ganglia did not appear much enlarged but the ganglia themselves were greatly increased in size up to the sixth cervical and there was some difference in size on the two sides. On section the nerves resembled a tendon. Microscopically the nerves showed practically all of their fibers to be swollen and there was an excess of nuclei. Between the nerve fibers and separating them lay masses of non-nucleated substance which stained deep yellow with van Gieson's counter stain. These masses were more numerous in the proximal portions of the nerves, whereas degeneration of myelin was more evident in the distal portions. The authors believe these masses to originate in hypertrophy of the sheaths of Schwann. They fail to find any of the "onion bulb" masses which are supposed to be characteristic. They designated the homogeneous masses as "plastic swellings." Scharlach R. preparations showed a small amount of fat in the swellings. The interstitial tissue was also hypertrophied and the bloodvessels in the nerves were thicker than normal, the adventitia especially being involved. The spinal ganglia revealed similar lesions but the interstitial hypertrophy was not so great. The authors believe that in these preparations they could trace the

origin of the substance from cells of the sheath of Schwann and they found the usual degenerative changes in the ganglion cells. The nerve roots were well myelinated and showed only very early plasmatic swellings. The cauda equina showed more extensive lesions than the other nerve roots. The spinal cord showed degeneration in the posterior columns only in the very lowest segments. Anterior horn cells in the cervical and lumbosacral enlargements showed a few cells displaying signs of central chromatolysis. The muscles showed irregular atrophy and the vessels were slightly thickened. The authors call attention to the similarity of their case to the original descriptions of Dejerine and Sottas. The presentation is a polyneuritic symptom picture with wasting, weakness and sensory loss of peripheral distribution. Pupils small and reacting sluggishly to light. (The authors consider the Argyll-Robertson pupils in the second case of Dejerine and Sottas to have been due to the lues.) Course fibrillation and partial R. D. were present as was lancinating pain. Family histories and clinical courses were very similar. The authors stress their belief that the myosis observed in most cases in the literature is due to involvement of the cervical sympathetic fibers in the first thoracic roots. The great difficulty of detecting the hypertrophy of the nerves during life is emphasized. "Thus of the two signs which have come to be regarded in some of the modern textbooks as characteristic of the malady, one, the Argyll-Robertson pupil, is shown to have no value; the other, hypertrophy of the accessible nerves, may be inconspicuous, and may be observed only if especially looked for."

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**Psychology and Psychiatry in Industry. The Point of View of a Psychologist.**—VITELES (*Mental Hygiene*, 1929, 13, 361) believes that psychology has much more to offer industry than has psychiatry. He holds that the development of psychology along empirical laboratory and experimental lines has lead the psychologist to a scientific viewpoint that is lacking in the psychiatrist. He cites a large number of contributions which psychology has made to the understanding of accidents, the effect of monotony on production, the training of workers and so on, to show that the method of psychology is objective. He states that, "The psychiatrist still leans heavily upon uncontrolled conditions; upon observations not subjected to careful measurement; upon interpretations of mass data that may be too largely influenced by a point of view, representing rather the bias of the individual worker than a general principle subjected to verification through controlled observation of random, unselected samplings." What he considers the ineffectiveness of psychiatry in industry, he believes to be due to the carrying over into normal relationships the viewpoint acquired by prolonged contacts with abnormal patients. He calls attention to the fact that it is only very recently that psychiatry has had any dealings with the normal, whereas psychology has concerned itself from the outset in attempts to understand normal people and normal behavior. (One gathers from the entire article that while the author's criticisms are unquestionably just to some extent, he has missed the essential point of the application of psychological and psychiatric approaches to industry. One would not expect the two sciences to make the same contribution and his spirit of rivalry and jealousy is unfortunate.)

## PATHOLOGY AND BACTERIOLOGY

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**Contributions to the Study of the Action of Ultraviolet Rays on Experimental Tuberculosis of the Guinea Pig.**—NASTA and BLECKMANN (*Arch. roum. de pathol. exper.*, 1928, 1, 353) have demonstrated in guinea pigs, infected with experimental tuberculosis, a diminution in sensitivity to the intradermal tuberculin reaction, which was very marked for the irradiated skin areas, yet distinct in those regions not directly exposed to the rays. The general response was also less when tuberculin was injected intraperitoneally, although attended by a febrile reaction. Large doses of tuberculin which killed the control, nonirradiated animal in less than an hour were not fatal to the irradiated guinea pig. These differences of reaction were absolute only for the early stages of the disease. The tissue-defense reactions following the reinoculation medium doses ( $\frac{1}{56}$  to  $\frac{1}{56}$  mg.) of tubercle bacilli appeared to show an activation in the irradiated animals, where the resultant abscess appeared earlier and was more rapidly replaced by a fibrous healing nodule. In one instance, a second reinoculation with large doses ( $\frac{1}{16}$  mg.) of tubercle bacilli resulted in only slight edema and transitory abscess formation with complete healing in the irradiated guinea pig, whereas the nonirradiated animal showed ecchymoses and subsequent formation of a nonhealing slough. A moderate and lesser leukocytosis and less accentuated polynucleosis, compensated by a slight increase of lymphocytes, were the characteristics which distinguished the blood picture of the irradiated tuberculous guinea pigs from that of the nonirradiated, tuberculous controls. A certain retardation in the progress of the lesions, with a longer span of life was observed in the irradiated tuberculous animals, compared with the nonirradiated controls. In view of their results, the authors feel that certain at least of the reactions known as allergic are neither the active factors nor in all cases the real indicators of the immune state.

**Races of Meningococcus and Antimeningococcus Serum Therapy in Roumania.**—NICOLAU (*Arch. roum. de pathol. exper.*, 1928, 1, 155) has reported the bacterial incidence, together with the methods and results of serum therapy of an epidemic of cerebrospinal meningitis, attacking Bucharest during the winter of 1922-1923. The method of isolation of the meningococcus which proved most satisfactory, consisted in sowing directly the cerebrospinal fluid, or the residue of its centrifugation on solid media (gelose-ascites, gelose medium of T. Nicolle). As determined by agglutination tests in 33 cases studied,

origin of the substance from cells of the sheath of Schwann and they found the usual degenerative changes in the ganglion cells. The nerve roots were well myelinated and showed only very early plasmatic swellings. The cauda equina showed more extensive lesions than the other nerve roots. The spinal cord showed degeneration in the posterior columns only in the very lowest segments. Anterior horn cells in the cervical and lumbosacral enlargements showed a few cells displaying signs of central chromatolysis. The muscles showed irregular atrophy and the vessels were slightly thickened. The authors call attention to the similarity of their case to the original descriptions of Dejerine and Sottas. The presentation is a polyneuritic symptom picture with wasting, weakness and sensory loss of peripheral distribution. Pupils small and reacting sluggishly to light. (The authors consider the Argyll-Robertson pupils in the second case of Dejerine and Sottas to have been due to the lues.) Course fibrillation and partial R. D. were present as was lancinating pain. Family histories and clinical courses were very similar. The authors stress their belief that the myosis observed in most cases in the literature is due to involvement of the cervical sympathetic fibers in the first thoracic roots. The great difficulty of detecting the hypertrophy of the nerves during life is emphasized. "Thus of the two signs which have come to be regarded in some of the modern textbooks as characteristic of the malady, one, the Argyll-Robertson pupil, is shown to have no value; the other, hypertrophy of the accessible nerves, may be inconspicuous, and may be observed only if especially looked for."

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the races of meningococcus were represented in the proportions of types A, 70.7; B, 25.0; C, 0.0; D, 4.3 per cent. In the treatment of the cases, antimeningococcic serum was injected into the spinal canal, the meninges, or the lateral ventricles, the injections being continued each day until the cytobacteriologic examination of the spinal fluid showed the desired picture. This consisted in diminution of the polymorphonuclear leukocytes; a normal appearance of the remaining leukocytes, with the absence of nuclear changes; absence of meningococci or very rare intracellular microbes. The continuance of the treatment beyond this point results in signs of meningeal intolerance. The clinical course is not a sufficient guide as to the course of serum therapy. In a total number of 35 treated cases, of which 9 were infants, 6, that is 17 per cent, died. The mortality for untreated cases in Roumania is 64 per cent. The author emphasizes the value of suspending serum therapy at the indicated time, the introduction of the serum in direct contact with the lesion and the use of interventricular injections in the fatal meningoventriculitis of infants as important aids to the reduction of the mortality of the disease.

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**Appearance of a Desensitizing and Hypotensive Substance in the Organism after Blockage of the Reticuloendothelial System.**—MOLDOVAN (*Arch. roum. de pathol. exper.*, 1928, 1, 167) has studied the functions of the reticuloendothelial system in experimental animals during the state of blockage of the endothelial cells, caused by the accumulation of granular material in their protoplasm following the injection into the circulation or peritoneal cavity of various substances, such as trypan blue, lithia carmin, colloidal metals and india ink. The experimental blockage of the reticuloendothelial system was followed after an hour, by the appearance in the circulation of a substance, which, when injected into sensitized guinea pigs, immediately before the administration of the intoxicating dose, protected them from anaphylactic shock. This desensitizing substance persisted in the circulation of the injected animal for a period of fourteen days. The active substance of the serum could be isolated chemically without impairing its activity. It proved thermoresistant, stable, soluble in acids, alcohol and water, dialysing readily across collodion membranes which did not permit the passage of protein substances. It was possible to titrate the protective dose of the isolated principle in a series of sensitized guinea pigs. The author regards this desensitizing substance as a product of internal secretion of the reticuloendothelial system. The serum obtained by the method of blockage possesses also a hypotensive action, which does not always run parallel with the antianaphylactic property. Sera containing the latter principle have been used with some success in clinical cases of hypertension where their administration was attended by a fall of blood pressure, occurring in five minutes, reaching its maximum in thirty to sixty minutes, and prolonged in effect for two to twenty-four hours.

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**The Arterial Supply of the Kidney in Nephritis.**—BAEHR and RITTER (*Arch. Path.*, 1929, 7, 458) have been able to demonstrate by injection methods a very considerable reduction in the smaller arterial and arteriolar divisions of the vascular tree in chronic diffuse nephritis.

They consider the inflammatory changes in the vessels to be relatively important in the production of the final contracted state of the organ. The study of four cases of early diffuse glomerulonephritis failed to reveal as yet any gross alterations in the arterial supply of the kidney.

**Experimental Paratyphoid Infection by Mouth under Various Living Conditions.**—Many attempts have been made to explain the outbreaks of paratyphoid epidemics in summer and autumn and also the infections following mild intestinal inflammations. In the pursuit of some explanation of these facts certain conditions controlling the pathogenicity of paratyphoid bacilli by feeding them to mice, rats and guinea pigs were determined by SEIFFERT (*Arch. f. Hyg. u. Bakteriolog.*, 1929, 101, 117). The pathogenicity was found to depend on two components: the ability to colonize in the intestine and the ability to pass through the intestinal wall. He considered the intestine the most important portal of entry, although highly virulent germs may establish infection from the oral cavity. The development of these bacteria in the intestine is helped if the animals are kept at temperatures of 28° to 32° C. and further, paratyphoid strains which disappear normally are thus enabled to become established. The second component which makes possible the parenteral invasion is favored by noninfectious inflammation of the intestinal mucous membrane (by feeding bile) or by raising or lowering the surrounding temperature, but changes in the food had no influence. The invasion depends on the injury of the mucous membrane by the germs which are pathogenic by feeding and apparently at ordinary temperature this injury is not enough to permit the invasion of the ordinary intestinal flora which does occur, however, if the surrounding temperature is kept high long enough. Paratyphoid bacilli can on occasion enter the tissues in a few hours and are recoverable from the mesenteric glands, liver and spleen. The outcome of the infection depends upon the virulence of the strain, and the defence power of the body. This latter can be raised by stimulating the reticulo-endothelial system. The body is able to render the bacilli harmless not only by destroying them but also by changing them into weakly virulent forms.

**Vaccination against Tuberculosis with Bacillus Calmette-Guerin.**—This paper by RANKIN (*Canadian J. Res.*, 1929, 1, 48) covers work on B. C. G. vaccine carried on in Alberta over a period of approximately four years, during which time some 250 calves were made the subject of experiments. The vaccine was found to be entirely harmless, vaccinated calves developing normally and showing at autopsy no tuberculous lesions. Vaccinated animals in most cases reacted subsequently to the tuberculin test. Calves vaccinated with B. C. G. and immediately exposed to infection showed moderately increased resistance to tuberculosis over unvaccinated controls. Calves vaccinated with B. C. G. and subsequently kept under sanitary conditions for a period, in order to permit resistance to develop before exposure to infection, showed 80 per cent immunity as compared with 14 per cent for the controls. The tuberculous lesions found in vaccinated calves were in general much less pronounced as well as less numerous than those in unvaccinated animals.

## HYGIENE AND PUBLIC HEALTH

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**The Causes of Illness at Different Ages. Hagerstown Morbidity Studies No. VII.**—SYDENSTRICKER (*U. S. Pub. Health Rep.*, 1928, 43, 1067), in a study at Hagerstown, Maryland, found that the respiratory diseases are the highest at all ages, and the highest point of this group is reached in the early years of life, declining rapidly to about the age of twenty years and then gradually increasing. Infectious diseases fall rapidly from the earliest years of life. From twenty-five years on they are a minor factor. In old age, organic diseases of the circulatory, nervous and urinary systems predominate. Adolescence and young adult life are the most favorable periods as regards nearly all classes of disease.

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**The Epidemiology of Undulant (Malta) Fever in Iowa.**—HARDY (*U. S. Pub. Health Rep.*, 1928, 43, 2459) has collected clinical, laboratory and epidemiological data on undulant fever. The diagnosis was based on serologic tests confirmed by clinical findings. The latter were, briefly, as follows: Insidious onset, weakness, profuse night sweats, chilliness, and rigors in some cases. Headache, backache, and joint pains were common. Constipation was the rule. The temperature was irregular and intermittent, usually with morning remissions often to normal. Only about one-third of the cases gave definite undulations with periods of freedom from fever. There was progressive loss of weight and anemia. The usual complications of undulant fever were observed. The diagnosis has been established in 83 cases in Iowa in a period of a little over one year. They were widely distributed throughout the state; twice 2 cases occurred in the same family. The largest number of cases occurred among farmers or persons living on farms. The number of males was 63 and the number of females 20. If one takes the cases that had no contact with live stock these are found to be equally divided between males and females. The cases occurred chiefly between the ages of twenty and fifty years. Hogs and cattle appeared to be the chief sources of infection; some cases seemed undoubtedly to be due to the use of milk from abortus infected cattle, others were clearly due to handling of infected stock, cattle or hogs, and one small group occurred among packing-house employees and seemed to be due to handling of infected slaughter-house products.

The findings are compared with those of Madsen, of Denmark, who found 122 cases of undulant fever among 2500 samples of blood examined which had been sent in primarily for the Widal test. In both series of cases children are strikingly immune, a fact difficult to reconcile with the theory that any considerable number of cases are due to the use of infected milk.

**The Pathogenicity of Morgan's Bacillus: A Series of Thirteen Cases Attributable to Infection with this Organism.**—Ever since the discovery of Morgan's bacillus in 1905 (*Brit. Med. J.*, 1906, i, 908) its significance has been uncertain. Morgan attached some importance to it as a cause of summer diarrhea, although he could demonstrate no antibodies in the patients' serum nor could he show that the organism was pathogenic for animals. The bacillus has a wide distribution in Nature, having been isolated from soil, roaches, mice and cows, as well as healthy and sick children. The lack of serologic unity between strains has also been cited as evidence against its etiologic relationship to the diseases in which it has been incriminated. On the other hand, there is evidence that Morgan's bacillus assumes, under certain conditions, a pathogenic rôle. It has been described as the cause of pyelitis, ulcerative colitis, fatal cholecystitis and fatal septicemia. In the present paper HAVENS and RIDGWAY (*J. Prev. Med.*, 1929, 3, 159) describe a series of 13 cases which have sufficient symptoms in common to constitute a recognizable clinical picture. In all of these cases evidence exists that Morgan's bacillus was the cause of the disease. Characteristic of all were the sudden onset, usually with a chill, and the equally abrupt termination, often by crisis. The duration was fairly constant, averaging about two weeks. Nausea and vomiting often accompanied the beginning of the attack, but other gastrointestinal symptoms were absent, with the exception of a mild diarrhea in 5 of the cases. Headache and general myalgia were conspicuous symptoms in all. Fever was always present, the temperature rising sharply at the onset and falling rapidly at the termination. Usually the temperature was only moderately high and fairly constant from day to day, with rather marked morning remissions. There was no indication of concentration in any age group; no cases in young children were discovered. The condition resembles paratyphoid infection clinically, and is very similar to Brill's disease, as it occurs in the Southern United States. The abrupt onset, the duration, the general aching and the rapid convalescence are characteristic, but the absence of any rash and the negative Weil-Felix test make this diagnosis unlikely. Morgan's bacillus appears to be the etiologic agent.

**Septic Sore Throat in 1928 in Massachusetts: Epidemiology.**—LOMBARD (*J. Prev. Med.*, 1929, 3, 81) states that there were between 925 and 975 cases and 48 known deaths in the epidemic of septic sore throat in Lee, Massachusetts, in July, 1928. The attack rate was 221 cases per 1000 inhabitants; the death rate was 9.6 per 1000 inhabitants. The epidemic was caused by the transmission, through raw milk, of hemolytic streptococci from the infected udder of a cow. The method by which the cow was infected is unknown, although some evidence

points toward a milk handler who was sick. Among the regular users of the infected milk the attack rate was greater in females than in males, but it shows no significant difference in the various age groups. The incubation period of the disease averaged two days. Over 90 per cent of the cases occurred within an interval of two weeks. Contact probably was responsible for less than 5 per cent of the total cases, but it is impossible to establish this definitely.

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**Postvaccination Tetanus and Its Prevention.**—ARMSTRONG (*J. Am. Med. Assn.*, 1928, 90, 738) states that epidemiologic evidence indicates that large insertions and the use of shields and dressings predispose to postvaccination tetanus in man. Shields and dressings markedly favor the development of postvaccination tetanus in monkeys and rabbits inoculated with a virus artificially contaminated with *B. tetani*. A proper vaccination is defined as one in which the insert is not more than  $\frac{1}{8}$  inch in its greatest diameter and which is made by some method that does not remove or destroy the epidermis. Such insertions, when treated openly, have never, as far as known, been followed by postvaccination tetanus.

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**A Comparison of the Mortality in a New England Colonial Town with that of Modern Times.**—RUSSELL and LUCIA (*Am. J. Hyg.*, 1929, 9, 513) chose for their study the town of East Haven for the period of 1773–1822 and the New Haven of today. They found that the cumulative curves of age distribution of the population of Connecticut during the past century show a marked rise in median age—from eighteen years in the 1800–1810–1820 population to twenty-seven years in the 1920 population. In the colonial population the greatest mortality occurred among children and young adults. At the present time, emphasis is being placed on improving the conditions in the lower age groups with the result that more individuals are saved for the period of productivity. The number of deaths under five has decreased somewhat, but the greatest improvement has been between the ages of fifteen and thirty-five years. For both modern and colonial times, the lowest mortality is at the age of twelve years, it being approximately two per thousand.

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OCTOBER, 1929

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ORIGINAL ARTICLES.

URINE FORMATION DURING THE ACUTE AND CHRONIC  
NEPHRITIS INDUCED BY URANIUM NITRATE. A CON-  
SIDERATION OF THE FUNCTIONAL VALUE OF THE PROXIMAL  
CONVOLUTED TUBULE.\*

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THE study of function in relation to structure is perhaps the oldest of the methods of physiologic inquiry. The employment of this method in the simplest organs and organisms has certain definite limitations, for by its use it becomes difficult to interrelate in terms of a balanced functional response of an organ as a whole the various activities of the histologic components of the structure. Furthermore, deductions obtained from this type of experimentation through reasoning from structure have of their nature to be inferential and can rarely assume absolute values. Even with this purposely minimized conception of the method's value, we do not have to go far into the past few years to appreciate the truths which it has established in regard to the thyroid gland through the researches of Marine,<sup>1</sup> in regard to brain cells in surgical shock and recuperation by Dolley,<sup>2</sup> in regard to the pancreas by Banting, Best and Macleod,<sup>3</sup> and in a recent one of these lectures by Aschoff<sup>4</sup> in regard to the kidney. When, however, this method which has been so abundantly fruitful in ascertaining the functions of other organs has been applied to the kidney the tendency has been to minimize the results obtained in a disproportionate fashion to their

\* Harvey Society Lecture, 1928-1929.

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minimization when secured from other organs. Such a skeptical attitude is to a certain extent justifiable. In the kidney of the higher animals there is not only such an intimate relationship between widely separated types of tissue which participate in a common function, but such a variation in the cytologic character of these units that it becomes difficult, if not impossible, at present, through injury to separate one from the other functionally. With such an appreciation of the difficulties which will be encountered and of the judiciousness which must be used in making inferential conclusions, I feel that as a result of over twenty years of continuous study certain estimates in terms of function can be made concerning the different elements of renal structure.

Uranium in the form of one of its salts is one of the oldest substances to be used to induce a renal injury either for the purpose of obtaining acute and chronic renal changes comparable to those developing in man, or for the purpose of inducing such changes and attempting to correlate the histologic findings with the renal functional response. In 1854 Leconte<sup>5</sup> first used uranium as a nephrotoxic agent. Much later than this Richter,<sup>6</sup> Chittenden and Hutchinson<sup>7</sup> and Chittenden and Lambeth<sup>8</sup> became interested in the action of uranium, and Wallace and Myers<sup>9</sup> investigated the ability of the substance to induce a glycosuria. Schirokauer<sup>10</sup> and Heineke and Myerstein<sup>11</sup> induced both severe vascular and epithelial injuries with it, and noticed the anasarca which followed its use. Christian,<sup>12</sup> Christian, Smith and Walker<sup>13</sup> and Christian and O'Hare<sup>14</sup> described in detail the renal epithelial injury, and also described the occurrence of hyalin droplets in the walls of the glomerular capillaries. Pearce<sup>15</sup> classed uranium along with the chromates as a substance which early in its action very largely localized its injury to the convoluted tubules. In several studies<sup>16,17,18,19</sup> from my laboratory the selective affinity of this substance for the tubular epithelium when used in dogs has been emphasized, and it has been furthermore pointed out that the age of the animal<sup>20</sup> determines in large measure the severity of the toxic response. Later than these observations studies were conducted in which it was shown that uranium induced a rapid reduction in the reserve alkali of the blood in normal animals,<sup>21</sup> in animals with a naturally acquired chronic nephritis<sup>22</sup> and that a protection against it could be established by the use of a weak alkaline solution or glucose.<sup>23,24</sup> The injury in such animals was largely confined to the convoluted tubules and the protection resulted in preserving to a greater or less extent the histologic structure of these cells. These observations were confirmed by Goto.<sup>25</sup> At a later period the work of Suzuki<sup>26</sup> and Mitamura<sup>27</sup> in Aschoff's laboratory gave exceptional emphasis to the specific localization of the nephrotoxic action of uranium and enabled them to formulate certain functional deductions during the acute injury.

The observations which are to follow have been obtained by rendering dogs acutely nephropathic by the use of one subcutaneous injection of 2 or 4 mg. of uranium nitrate per kilogram and attempting to correlate the histologic changes in the kidney during the acute nephritis, the stages of repair and over a period of four years after the animals had developed a chronic nephritis with certain functional expressions in the blood and urine. A number of these animals have effected by different histologic methods such degrees of renal repair that they either gave no evidence of a functional disturbance or such changes were slight in character. In such animals secondary injections of uranium have been used to ascertain its influence upon function when the cytologic basis for this restored function or functional improvement was again subjected to morphologic alteration by the use of uranium.

The evidence of renal functional depression during the acute and chronic nephritis and during periods of recovery have been obtained by studying the animals at various periods after they had been rendered pathologic and terminating the experiments when such changes in function had developed so far as to make it desirable to check a given expression of renal function with the changes then existing in the kidneys. The daily volume output of urine has been obtained, the amount of albumin in grams per liter and the relative number and character of the casts it contained have been noted.

Associated with these simple studies of the urine, the reserve alkali of the blood has been determined by the methods of Marriott<sup>28</sup> and van Slyke and Cullen<sup>29</sup> and the immediate functional value of the kidneys ascertained by the phenolsulphonaphthalein test of Rowntree and Geraghty.<sup>30</sup> Evidence of persisting renal dysfunction as shown by retention has been obtained by estimating the degree of urea nitrogen retention by the method of Marshall<sup>31</sup> as modified by van Slyke and Cullen<sup>32</sup> and nonprotein nitrogen and creatinin by the methods of Folin and Wu.<sup>33</sup>

The animals were given 500 cc. of water daily by stomach tube and fed on a mixed diet of bread, butter, meat and milk. In order to regulate to some extent the severity of the acute nephritis, animals varying in age have been used. It was hoped to induce in the older group of animals a more severe nephritis with but slight evidence of repair and functional restoration, while in the younger groups of animals there might be obtained from the same dosage of the nephrotoxic agent a less intense acute nephritis which would lend itself to changes of repair with the development of a chronic diffuse renal injury. A total of 72 dogs have been used in the experiments. On the basis of the acute response of these animals, both anatomically and functionally, as well as in terms of their ability to completely recuperate functionally or repair the kidney to a functional state indicative of a chronic nephritis, they may be divided into four groups.



Group I is represented by 21 dogs which either died during the acute stage of the nephritic process or were killed at various intervals of it for purposes of study and functional correlation.

Group II comprises 15 dogs which after having developed a severe acute nephritis returned to a complete functional normal.

Group III is made up of 36 animals, which, after having developed an acute nephritis, failed to make a functional adjustment back to the normal, but were left with such changes in the kidneys and gave evidence of such functional alterations in the blood and urine that they have been classed as animals with a chronic nephritis.

The animals of Group IV, 41 in number, were given an acute nephritis by the use of 2 mg. of uranium per kilogram. After they had either completely recovered functionally or recovered with the development of a chronic nephritis they were given a second injection of 2 or 4 mg. of uranium and the functional reaction in connection with the changes in the kidney studied.

In discussing the results obtained in these groups of experiments, it should be kept in mind that the functional studies were not terminal observations. Such observations were made on the respective animals at frequent intervals, as changed functional states demanded a study in connection with the pathology of the kidney from the commencement of the acute nephritis until the animals had established their pathologic normals in terms of a chronic nephritis, or, in cases of recovery, through this process and through the secondary uranium injury in case a secondary intoxication was employed.

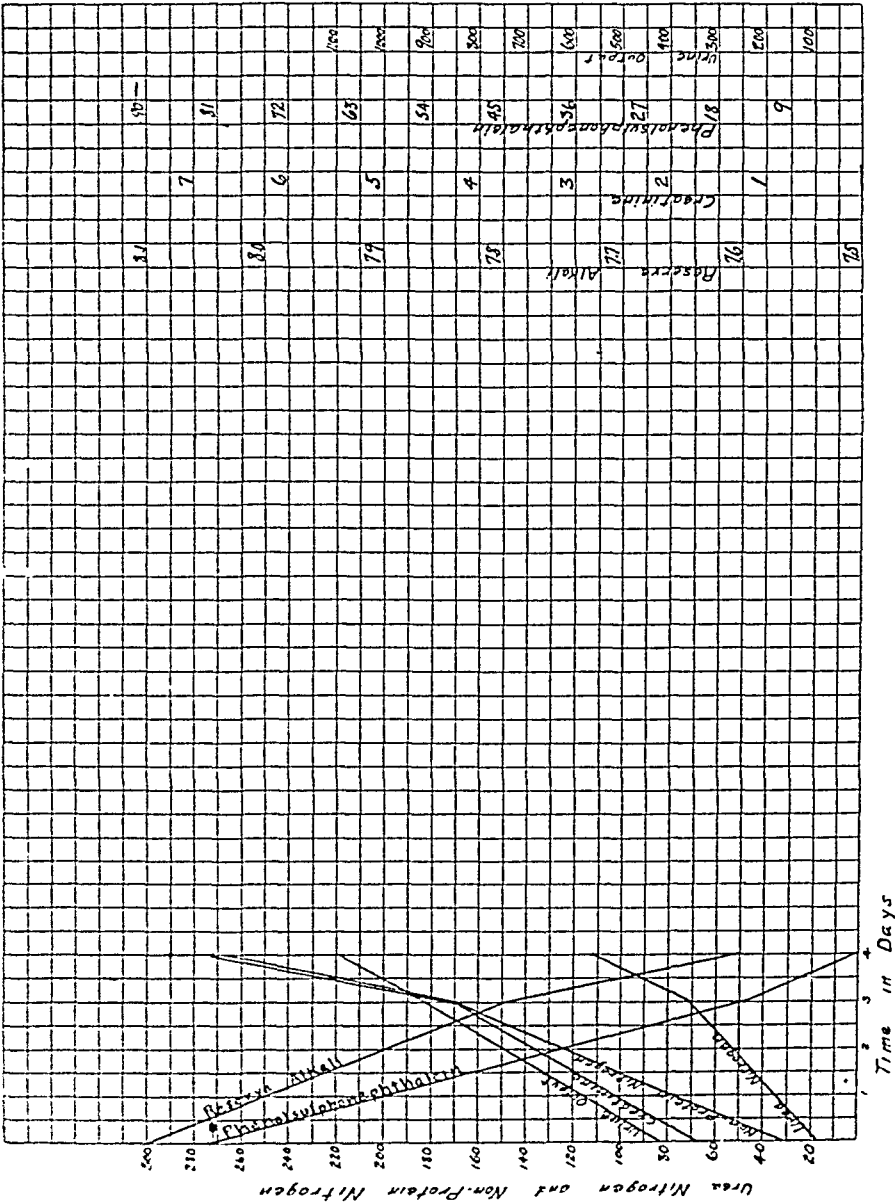
The dogs used in the first group were over seven years old. None of the animals survived the acute injury longer than fourteen days. From the commencement of the nephritis until its termination studies were made every other day or every third day of the functional disturbance in connection with the changes in the kidney. These studies have shown by the second day of the nephritis an increase in the output of urine over the 500 cc. of water intake, and the urine has contained from 1.2 to 6.8 gm. of albumin per liter with numerous granular casts. The maximum output of urine at such a time has been 1427 cc. The urine early in the nephritis contains glucose. With these changes in the volume output of urine there occurs a sudden reduction in the elimination of phenol-sulphonephthalein to a trace or to a negative elimination in a two-hour period and an equally sharp reduction in the alkali reserve of the blood. The reduction has varied from the normal of 8.1 to 7.85. Usually within twenty-four hours retention of blood urea begins, and later nonprotein nitrogen and creatinin, which by the sixth to the tenth day of the nephritis has reached 150 mg. of urea, 216 mg. of nonprotein nitrogen and 5.3 mg. of creatinin. During such periods of retention there is no change in the elimination of phenolsulphonephthalein and no attempt at a restoration of the

reserve alkali of the blood. Usually by the eighth day the amount of albumin has diminished without any change in the character of the casts, and toward the termination of the nephritis the volume output of urine may or may not be reduced below the water intake of the animal. This has very largely depended upon whether or not the animals retained the water.

In this, as in other groups of animals, the functional observations other than the output of urine are expressions of the histologic changes in the kidneys within an hour of the animals' death. The severity of the changes in the convoluted tubule epithelium in animals with this type of response, in which there was no attempt at recovery, have shown some variation in the respective animals, depending upon the duration of the nephritic process. The glomerular changes, however, have not shown the same degree of structural alteration as the duration of the nephritis progressed. These structures after the commencement of the renal injury have shown capillaries distended with blood, and the capillary endothelium has appeared prominent with deeply staining nuclei. Thrombosis of the vessels has not occurred, and only in the late stages of the process have exudates of any type been observed in the subcapsular spaces. There has been no hyperplasia of the capsular epithelium and no evidence of glomerular or periglomerular connective-tissue formation. The epithelium of the convoluted tubules has shown the selective action of uranium by developing an edema and necrosis, which varies in degree with the duration of the injury. It has been impossible for me to say that only definite segments of this tubule were involved in the injury. On the contrary, I believe that other tubules participate to some extent in the uranium reaction. This is slight as contrasted with the proximal convoluted tubule injury, and may be due to factors other than the direct action of this nephrotoxic substance. The cells of the descending limb of Henle's loop rarely if ever show evidence of injury. In 4 of the animals in this group obtained for autopsy between the fourth and tenth day of the nephritis occasional mitotic and premitotic figures were found in the degenerating material of the convoluted tubules. These changes, indicative of an attempt at repair which failed, were not observed in animals after the tenth day of the injury.

The functional expression of these lesions consists in the animal becoming polyuric with an albuminous urine containing granular casts. If the intake of water could be maintained the dogs persisted for as long as fourteen days in a polyuric state, the formation of urine equalling or exceeding the water intake. In those animals in which fluid was not retained there was a reduction in urine formation below the water consumption which was not associated with structural degenerative changes in the glomeruli. Associated with these changes in the volume output of urine there developed a definite relationship between the severity of the injury to the epithelium

of the convoluted tubules and the elimination of phenolsulphone-phthalein and the decrease in the reserve alkali of the blood. Soon after the commencement of this evidence of renal failure there occurs a progressive retention of urea nitrogen, nonprotein nitrogen and creatinin. No member of this group of animals showed any definite



evidence of tubular epithelial repair and in none was there any attempt at a restoration of renal function. (Charts I and II.)

A second group of animals of the series, but younger, between one and two years of age, were also given an acute nephritis by one subcutaneous injection of 4 mg. of uranium nitrate per kilogram and

[illegible]

## CHART II

with the processes of repair the functional value of these organs which finally resulted in their return to a state of normal renal function. From the commencement of the acute injury until such a normal response had been obtained the experiments were terminated at suitable periods to trace the transition from one of depressed function to one of normal function. In this group it furthermore

became necessary to know that in the kidney of a given animal there had existed a certain type of acute degenerative reaction associated with diminished renal function, and that in the kidney of this specific animal changes of repair had resulted in a return to normal function. For this purpose, in 8 of the animals before there was any functional evidence of recuperation after the kidney had been protected by a glucose solution<sup>34</sup> against the toxic action of the anesthetic, the dogs were anesthetized by morphin ether and a wedge-shaped piece of tissue removed from the upper pole of the left kidney. The animals recovered and finally returned to a functional normal. After such a state had developed the experiments were terminated and the kidneys studied in relation to the functional recuperation.

The renal changes in this group of dogs during the stage of acute nephritis are similar in location, though less severe than those previously described for the first group of animals in which no improvement in function was noted. The glomerular vessels were distended with blood. The capillary endothelium appeared prominent, with deeply staining nuclei. There were no subcapsular exudates. The convoluted tubule epithelium was edematous and showed early changes of necrosis. There was no evidence of regeneration. The cells of the descending limb of Henle's loop appeared normal. At this stage of the renal injury the animal of this experiment was forming 537 cc. of urine, which contained 0.5 gm. of albumin, numerous granular casts and a few hyalin casts. The elimination of phenolsulphonephthalein had been reduced to 5 per cent and the reserve alkali to 7.8. There was a retention of blood urea of 70 mg., nonprotein nitrogen 120 mg. and creatinin 4.75 mg.

The rapidity with which a functional recuperation takes place in these animals showed a marked degree of variation. The earliest return to a state of complete functional normal was on the nineteenth day following the commencement of the nephritis. The latest return to such a state was five months and twenty-two days from the date of the initial injury. With such a difference in animals in the time necessary for the development of a functional recovery there must have occurred in the same series of animals a variation in the severity of the acute injury, the development of a different type of renal repair, or both factors may have operated in the same animal. The histologic studies of the kidneys in animals which recovered show that in both the rapid and slow types of recovery the acute injury is characterized by but slight structural changes in the glomeruli. The degree of epithelial injury shows a variation and the dominant type of epithelial repair is entirely different in the animals which have varied so much in the length of time necessary to effect a return to normal function. In those animals in which a rapid resumption of renal function took place

the convoluted tubule cells were not lost. Following an injury associated with edema and moderately severe necrosis a regeneration of these cells took place from preëxisting cells. In animals in which there is a delayed period for functional recovery the epithelial replacement takes place to a minor degree by the process just described while the dominant type of repair is by an entirely different process. Many of the convoluted tubule cells which have become necrotic and have disappeared are replaced by these tubules becoming lined by a flattened, apparently less specialized cell with prominent and deeply staining nuclei. The tubular lining may have a syncytial-like appearance with imperfect cell differentiation.

On the twenty-fourth day of the nephritis in the animal under consideration there was an output of 400 cc. of urine which was free from albumin but which contained finely granular and hyalin casts. The elimination of phenolsulphonephthalein had increased from 5 to 45 per cent and the reserve alkali of the blood had increased from 7.8 to 8.1. The retention of blood urea was reduced from 70 to 15 mg., nonprotein nitrogen from 120 to 30 mg. and creatinin from 4.75 to 1.5 mg. With but slight variation from the normal, this type of response continued into the fifth month, when the animal became functionally normal. At the termination of the experiment the histologic study showed the glomeruli varying much in size and structure. Many of these units showed a connective-tissue obliteration of the loops, while other capillaries contained blood. The capsules showed a thickening which was variable and frequently the capillary tufts were in areas adherent to the capsule. The glomerular damage was not uniform.

The epithelium of the convoluted tubules showed two entirely different types of repair. The first type is characterized by the formation through regeneration from less severely injured convoluted tubule cells of an epithelial replacement very similar to cells normal for this part of the tubule. The second and more usual type of repair was by an entirely different type of flattened cell atypical for this location in the tubule.

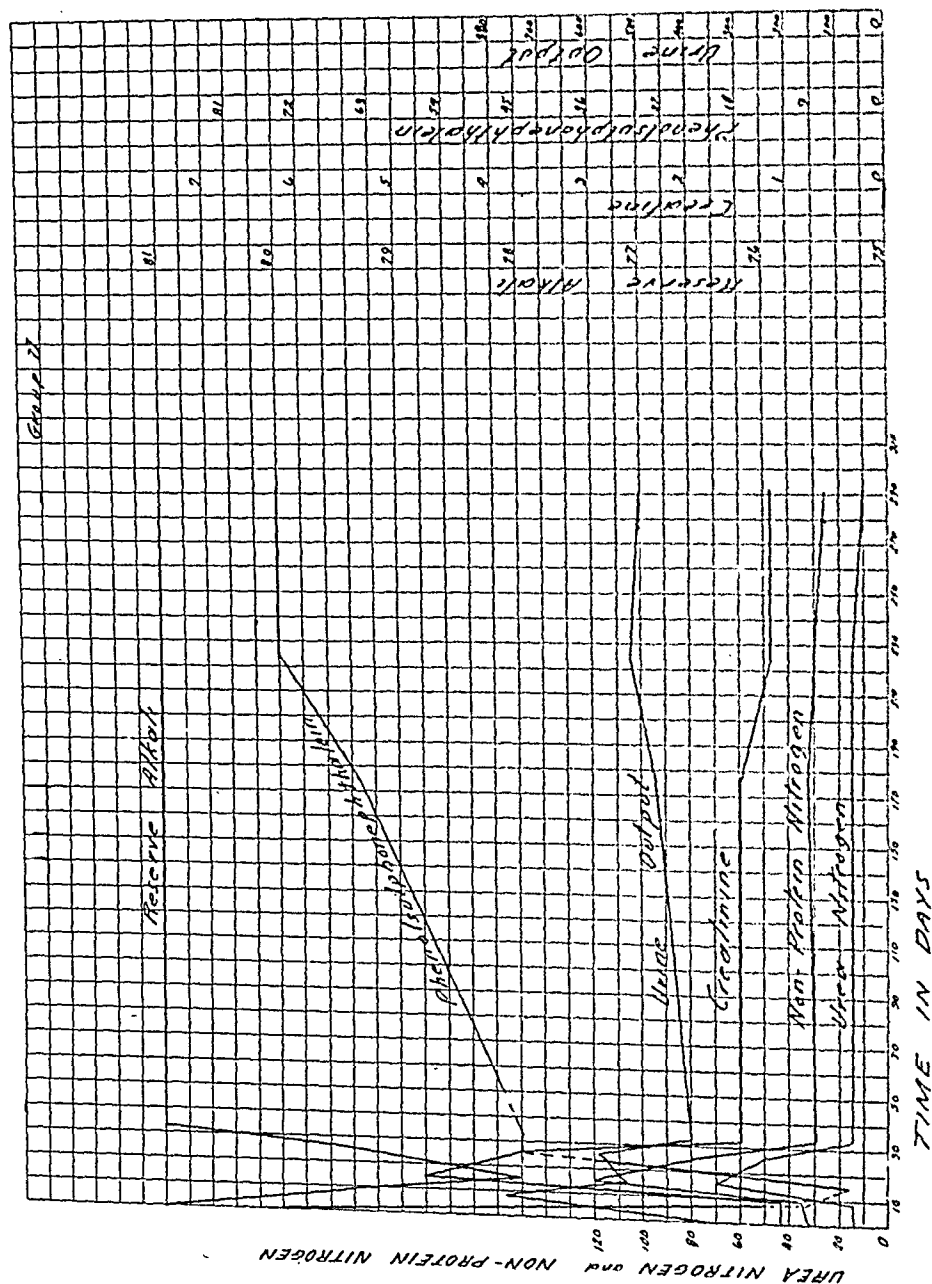
The animals in this series were young dogs between one and two years of age which developed, as did the older animals, a severe acute nephritis from uranium. The fact that such a condition existed was not only established by a functional comparison of the two groups, but by the removal from the kidney in certain of the animals of the latter group before any evidence of functional recuperation had commenced of tissue which served as a histologic control for a specific animal of the group. The changes in such control tissue consisted in an acute epithelial degeneration of the cells of the proximal convoluted tubules and with but only slight evidence of structural injury to the glomeruli. Later in the course of nephritis the epithelial regeneration of two entirely different types developed in the injured tubules. The glomeruli at this time

showed evidence of a preëxisting injury by the formation of connective tissue with the obliteration of capillary loops and thickening of the capsules. Connective tissue was formed in the periglomerular and intertubular areas.

The functional response shown by these animals during the acute nephritis and during the changes of repair with the establishment of a state of normal renal function are as follows: The animals became polyuric with an albuminous urine containing casts. There was a rapid reduction in the elimination of phenolsulphonephthalein, a decrease in the reserve alkali of the blood, a retention of urea, nonprotein nitrogen and creatinin. This response is similar up to a certain stage with the response obtained from the first group of animals which failed to recuperate. In the second series of animals changes of repair developed which enabled the dogs finally to return to a functional normal. The time limit for this process varied, but the character of the reaction was the same. This return to the normal was associated in all of the animals with a regeneration of convoluted tubule epithelium of two types. The dominant cytologic type regenerated in the different animals varied. At the same time that such processes of repair occurred in the tubules there developed fibrous-tissue changes of an obliterative character in the glomeruli which were not uniform in severity or distribution. The functional expression of such types of repair have consisted in a decrease in urine formation to or toward the animal's normal daily output, a decrease and final absence of albumin from the urine and with a change in the character of the casts from a granular to a hyalin type. In a certain number of the animals the casts disappeared. Associated with these changes in the urine there was a gradual increase in the elimination of phenolsulphonephthalein, a decrease in the depletion of the reserve alkali to the normal and a decrease in retention of urea nitrogen, nonprotein nitrogen and creatinin until these values reached the normal. (Charts III and IV.)

A final series of young dogs which were given 4 mg. of uranium nitrate per kilogram, after developing an acute nephritis, failed to effect a functional restoration, but were left with such histologic changes in the kidneys and such evidence of renal dysfunction that they could be classed as animals with a chronic nephritis. In this group of 38 dogs functional studies were made in connection with the histologic studies of the kidneys from a period of two days following the commencement of the nephritis, through the period of repair and for five years and four months into the stage of functional stabilization which may be looked upon as the animals' pathologic normal or chronic nephritic state. Both the functional and anatomic changes during the stages of acute nephritis and of repair resembled those of the second group of animals with the exception that the animals in the former group were able to establish a complete restoration of function while this last group of animals were unable to effect such a return to the normal. Eight dogs of

this group showing quantitatively the same type of response as other members of the group in the acute stage of the injury were anesthetized by morphin ether and renal tissue removed from the upper pole of the left kidney to serve as a control for the acute stage of the injury and for the subsequent stages of repair. The study



### Chart III

of such tissues in connection with the functional response of the animals when it was obtained showed the same type of degenerative changes as has been described in such dogs in the previous groups. The terminal studies were made in animals in which a chronic nephritis had existed for as short a time as four months and in other dogs over as long a period as five years and two months.



The study of the following animal is characteristic for the members of the group. On the sixth day of the acute nephritis the dog was polyuric, with an output of 1200 cc. of urine, which contained 2 gm. of albumin per liter and numerous granular and hyalin casts. There was no elimination of phenolsulphonphthalein in a two-

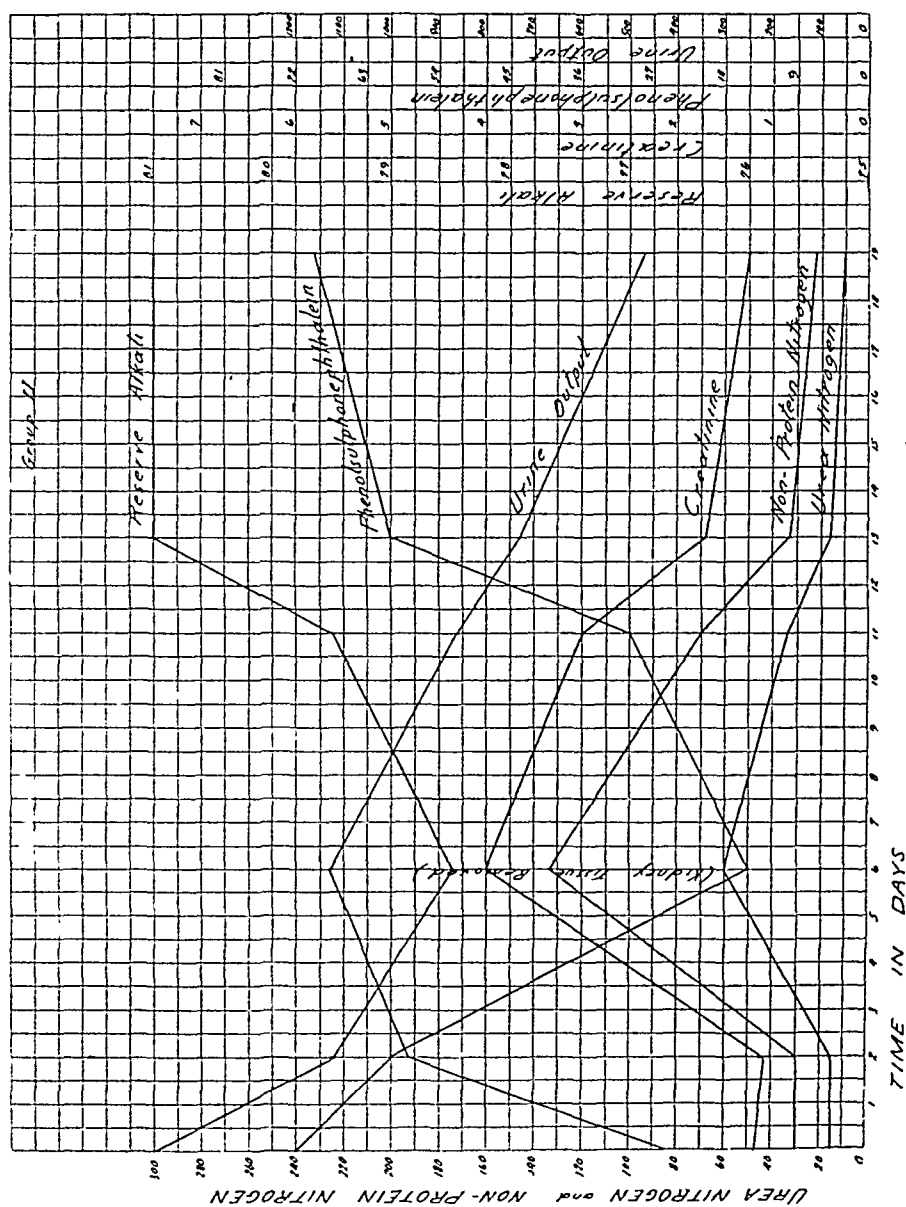


CHART IV

hour period, the reserve alkali was reduced from the normal of 8.1 to 7.8; there was a retention of 45 mg. of blood urea, 78 mg. of non-protein nitrogen and 4.6 mg. of creatinin. On the twenty-fifth day the amount of albumin had decreased but with little change in the number and character of the casts. There was a trace of phenolsulphonphthalein eliminated in a two-hour period and an increase

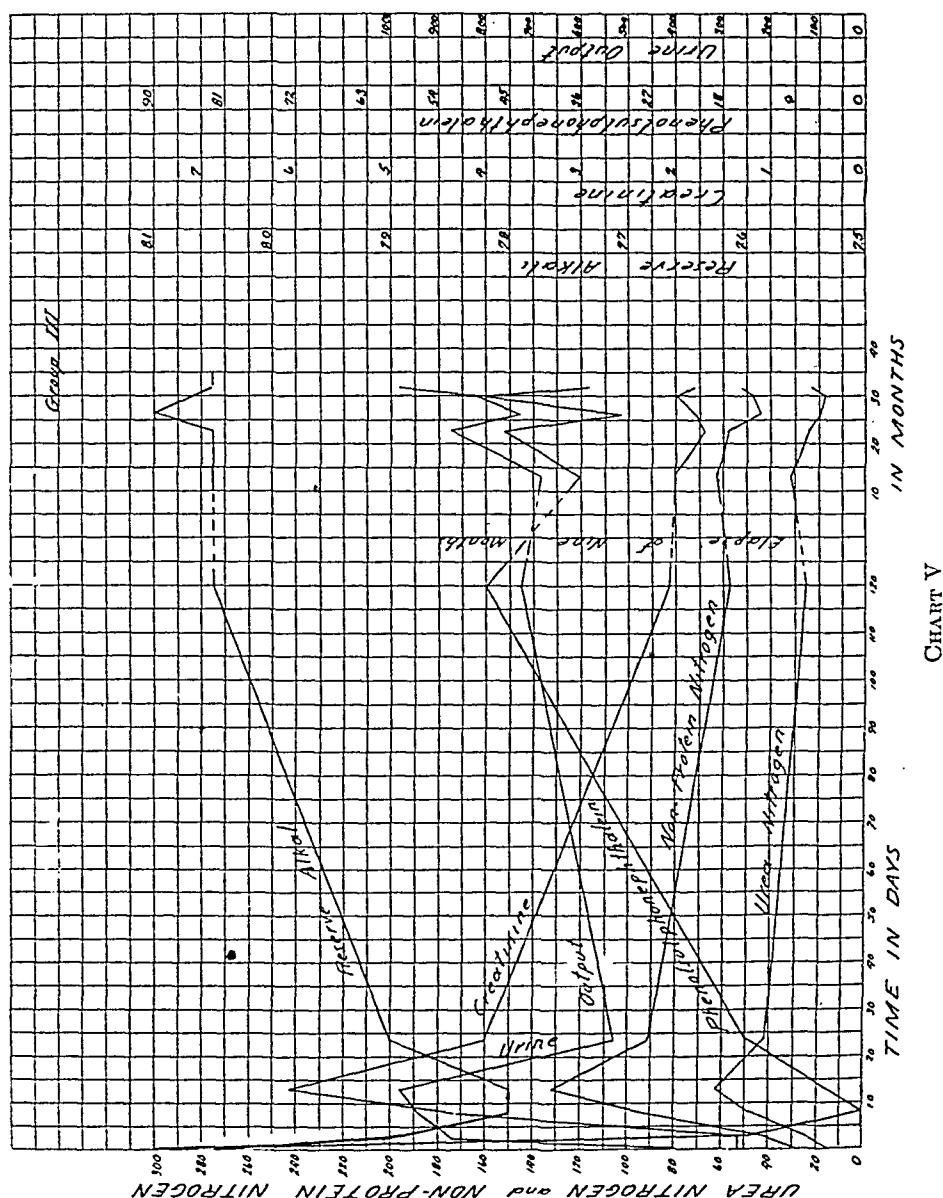
in the reserve alkali to 7.9. The evidence of retention had increased so that the blood showed 100 mg. of urea nitrogen, 128 mg. of non-protein nitrogen and 6.1 mg. of creatinin. On the thirty-fifth day of the experiment there was an output of 511 cc. of urine which contained albumin, but a decrease in the number of granular casts and a relative increase in the hyalin type. The elimination of phenolsulphonephthalein was 12 per cent, the alkali reserve of the blood had increased to 7.95, the retention of urea had decreased to 33 mg., nonprotein nitrogen to 50 mg. and creatinin to 3.1 mg.

From this period to the termination of the experiment, two years and three months from its commencement, the functional response of the animal varied but little. At this time, with an intake of 500 cc. of water, the dog was forming 811 cc. of urine, which contained albumin and hyalin casts. There was an elimination of 34 per cent of phenolsulphonephthalein, a normal alkali reserve of the blood of 8.1, a retention of blood urea of 30 mg., of nonprotein nitrogen of 54 mg. and creatinin 2.4 mg.

The chronic renal changes which developed as a result of an attempt at repair which failed to reestablish a state of normal renal function are as follows: The kidneys were small, with an irregular surface and the capsule thickened and adherent. On section, the kidney showed a decided thinning of the cortex. The histologic study showed a general glomerular fibrosis which varied in intensity in different glomeruli. All of these structures had participated in the reaction to some extent. Many of the capillary loops had been obliterated by connective-tissue formation. In some of the glomeruli this process was complete with a later hyalinization of the fibrous tissue. In other units this obliteration had been partial with the remaining loops with thickened walls containing blood. The glomerular capsules showed a connective-tissue thickening to which the fibrous capillaries were often adherent. Hyperplasia of the capsular epithelium was rarely observed. Many of the tubules had disappeared, with a replacement of masses of fibrous tissue. The smaller arteries with thickened middle coats were numerically prominent. The convoluted tubules which remained were lined by two types of cells. The first type, in which degenerative changes were still occurring, had in general the appearance of convoluted tubule epithelium. Such cells appeared normal or more usually they had a granular structure, stained imperfectly and in many instances the nuclei were hypochromatic or had disappeared. This type of cell is likely one of the regenerated types previously described, many of which have later undergone processes of degeneration.

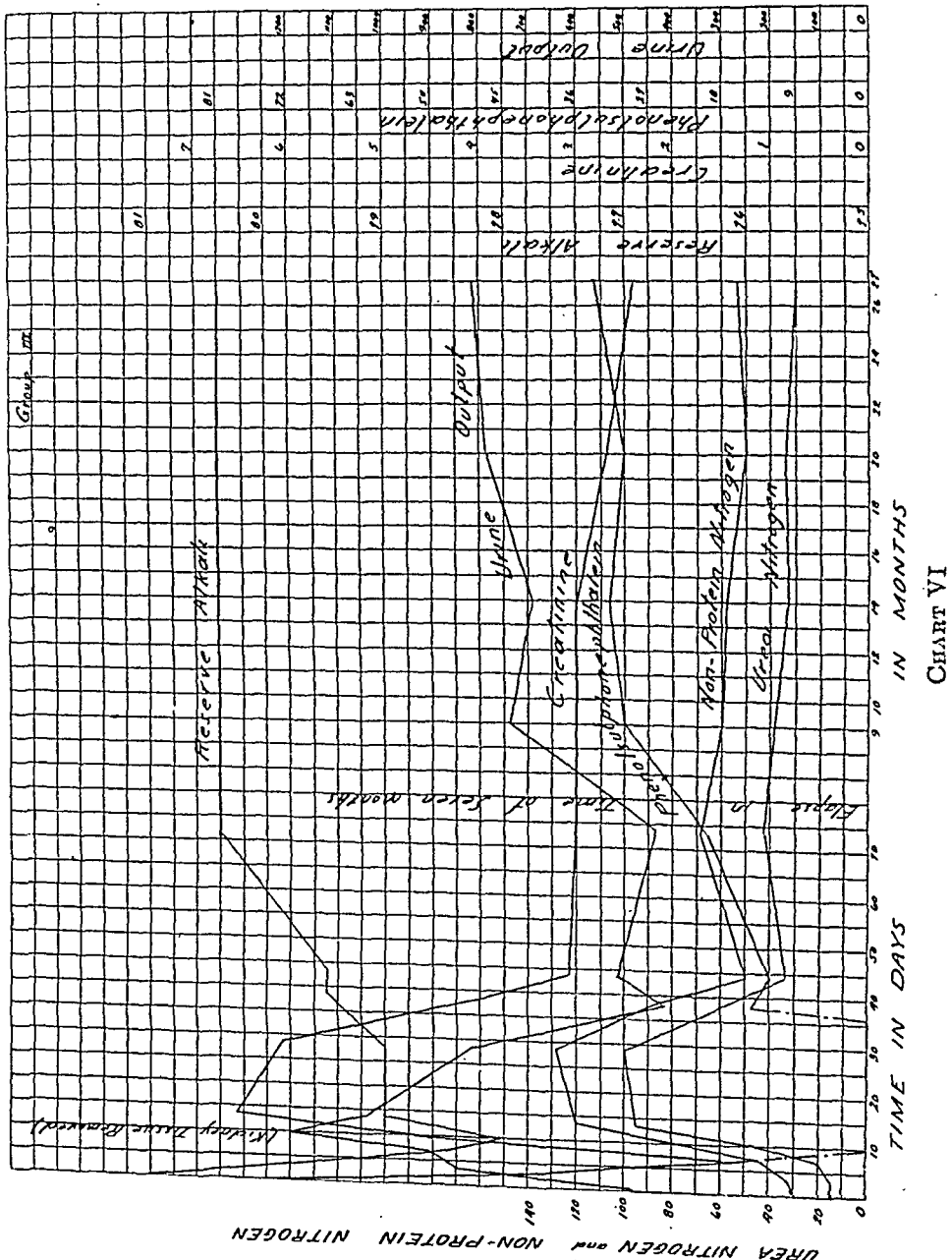
The second and usual type of cell to be found in the convoluted tubules at such a stage of repair with the development of a chronic nephritis is a regenerated cell of an entirely different order. The epithelium is in the form of a cytoplasmic layer which may or may

not be differentiated into cells with definite cell boundaries. They line the tubules with a low flattened type of epithelium with large, deeply-staining nuclei. They do not have the specialization in histologic structure characteristic of proximal convoluted tubule epithelium. The cell is atypical for this part of the tubule. (Charts V and VI.)



In connection with the terminal pathology shown by these dogs as well as by the same animal and other animals of the group before the development of the terminal changes, it becomes desirable to review the sequence of the functional response shown by the dogs of the group. As early as the second day following the development

of an acute nephritis the animals became polyuric, with an albuminous urine containing granular casts. There was a marked reduction in the elimination of phenolsulphonephthalein, or it failed to appear in the urine in a two-hour period. The reserve alkali of the blood was reduced to as low as 7.8 and a retention occurred in blood urea,



nonprotein nitrogen and creatinin. At such periods of renal functional depression there was slight evidence of structural glomerular injury and marked evidence of proximal convoluted tubule degeneration with early necrosis. The severity of these functional changes increased to a period in the respective experiments which varied between the sixth to the sixteenth days. At such periods

the amount of albumin and number of granular casts diminished, phenolsulphonaphthalein reappeared in the urine or increased in its percentage elimination, the reserve alkali of the blood increased and the retention of urea, nonprotein nitrogen and creatinin diminished. Such functional expressions of improvement were anatomically associated with epithelial regeneration in the proximal convoluted tubules and the commencement of structural changes of a chronic degenerative character in the glomeruli. During the months, and finally the years, following the commencement of such changes the urine output usually remained above the intake of water, and the amount of albumin and the number of finely granular and hyalin casts decreased. The amount of phenolsulphonaphthalein eliminated has increased to as much as 35 per cent, the reserve alkali of the blood returns to the normal and the degree of retention of urea, nonprotein nitrogen and creatinin, while diminishing, failed to return to the normal. Correlated with this improvement in renal function and the establishment of the respective animals of their pathologic normal, there was a continuation of epithelial regeneration and replacement in the convoluted tubules of an atypical type of epithelium for this location and a regeneration of a normal type of cell which frequently gives evidence of degeneration. Associated with this type of repair to the tubules, which is interpreted as a cytologic attempt at functional restoration, there developed a continuation in the processes of glomerular destruction which had not been uniform in intensity but which in many of these bodies had resulted in complete fibrosis and subsequent connective-tissue hyalinization.

This group of dogs, unlike the animals of the second group, failed to establish a functional normal. In those animals of the second group, in which the recovery period was delayed, the same type of process developed in the kidney but differed from the process in the third group with a chronic nephritis in that regeneration of both types of epithelium was a more prominent feature of the repair process and glomerular injury and obliterative changes in the smaller renal arteries was a less marked feature. The suggestion is offered that the reason for the imperfect epithelial regeneration and its maintenance in a state of functional effectiveness in the animals with a chronic nephritis is due to a final predominance of the injury to the glomeruli and smaller renal arteries.

As a result of these studies which have extended over a period of nearly six years, and which have been controlled in groups of animals and, furthermore, in the same animal by anatomic observation in relation to function disturbance, it becomes extremely difficult not to ascribe certainly to the proximal convoluted tubules a secretory function from without in, rather than to ascribe to them only the function of secretion or absorption from within out of substances formed at the glomerulus and found in their tubular urine.

It will be recalled from an earlier part of this discussion that a certain number of animals after they had recovered from the acute nephritis so extended the processes of renal repair as to make a complete functional recovery. This recovery was associated with early connective-tissue changes in the glomeruli and their capsules, in the periglomerular and intertubular spaces and were common for all of the animals which recovered. As these changes progressed, the type of convoluted tubule repair which predominated in the animals showed a marked difference. In certain animals of this series the convoluted tubules were repaired by the regeneration of an epithelium closely resembling that which is normal for such tubules. In other animals, although this same type of repair developed, the dominant type of regeneration and in areas the only type found was of a flattened, much less specialized cell with prominent nuclei. Suzuki<sup>35</sup> first made the observation that this type of cell was resistant to uranium. Somewhat later, and without knowledge of Suzuki's work, a similar observation was made in my laboratory, and, in addition, it was shown that such an epithelial lining of the convoluted tubules which were found in areas of repair in the kidney of dogs with a naturally acquired chronic nephritis were resistant to the general anesthetics as well as to uranium.<sup>36</sup> Gil and Gil<sup>37</sup> and Hunter,<sup>38</sup> in much later observations studied the histogenesis of such epithelial replacements and their resistance to uranium. In order to obtain more information concerning the resistance of renal epithelium to uranium and with the hope of strengthening the observations previously made concerning the functional value of convoluted tubule epithelium the following experiments were undertaken:

A group of 41 dogs (Group IV) were given an acute uranium nephritis by the subcutaneous injection of 2 mg. of uranium nitrate per kilogram and their functional response studied during the course of the acute renal injury and the period of repair. After these animals had returned to a functional normal a certain number were anesthetized by morphin ether and a wedge of renal tissue removed to check the then existing histologic changes with the functional return and to ascertain the type of epithelial repair which had been associated with the reestablishment of renal function. Such material also served as a control for subsequent changes developing in the kidneys of a given animal. This tissue has shown in different animals the two types of epithelial repair which have been previously described—either a predominant type resembling normal convoluted tubule epithelium or the flattened type which is atypical for this portion of the tubule. After having established the type of tubular repair which predominated in the animals the animals were given a second subcutaneous injection of either 2 or 4 mg. of uranium nitrate per kilogram. The functional response of these two groups of animals with a similar type of glomerular injury, but with predominatingly dissimilar types of epithelial repair were

entirely different. Those animals which had effected an epithelial repair by the regeneration of renal epithelium closely resembling morphologically that of the normal proximal convoluted tubule reacted functionally in a manner similar to, though more intensely than they did from the initial injection of uranium. The urine contained as high as 7.2 gm. of albumin per liter. The elimination of phenolsulphonephthalein was rapidly reduced to a trace or fails to appear in the urine, the reserve alkali of the blood was brought to as low as 7.7 and there developed the usual marked retention of urea, nonprotein nitrogen and creatinin. A certain number of these animals failed to survive the second injection of uranium. They developed an air hunger with or without convulsions. The changes in the kidney were similar to or more severe than the acute injury obtained from the primary use of uranium. The glomerular changes were similar to those noted after the recuperation from the initial acute nephritis and, in addition, showed an acute engorgement of the patent capillaries with blood and rarely a subcapsular exudate. The changes of degeneration in the repaired or regenerated convoluted tubule cells consisted in edema, vacuolation and extensive necrosis. In cells which remained attached to the basement membrane evidence of an attempt at repair was noted in the occurrence of mitotic figures. The dogs of this series which recuperated from the first injection of uranium and as a part of the process of repair regenerated an epithelium, similar to convoluted tubule epithelium, show no resistance to a second intoxication by it.

In the second group of animals the establishment of a functional normal was associated with a similar type of chronic injury to the glomeruli, as has been described for the first group, and by the regeneration in the proximal convoluted tubules of two entirely different types of cells. The first type resembles cells which are usual for this portion of the tubule and which have been shown to have no resistance for uranium. The second type, which has been the predominant form of regeneration in this group of animals, is of the atypical, flattened type of cell. When a second subcutaneous injection of 2 or 4 mg. of uranium was given to an animal with this type of epithelial repair to the convoluted tubules the functional response of the animal was entirely different from that of those of the first group. In this latter group there is a transitory increase in the formation of urine which has not contained over 1.3 gm. of albumin per liter with a small number of granular and hyalin casts. The elimination of phenolsulphonephthalein was but slightly reduced and the reduction in the reserve alkali of the blood has either failed to occur or it was not reduced below 8. There was no appreciable increase in the retention of urea, nonprotein nitrogen and creatinin. Following such slight changes in renal function from the secondary injection of uranium, the animals returned to the state of renal functional response previously established from the

primary injection of uranium. The kidneys of such animals showed in the glomeruli an increase in the degree of fibrosis over that observed following the changes of repair secondary to the first acute nephritis from uranium. The convoluted tubules showed three types of changes. The majority of the tubules were lined by the

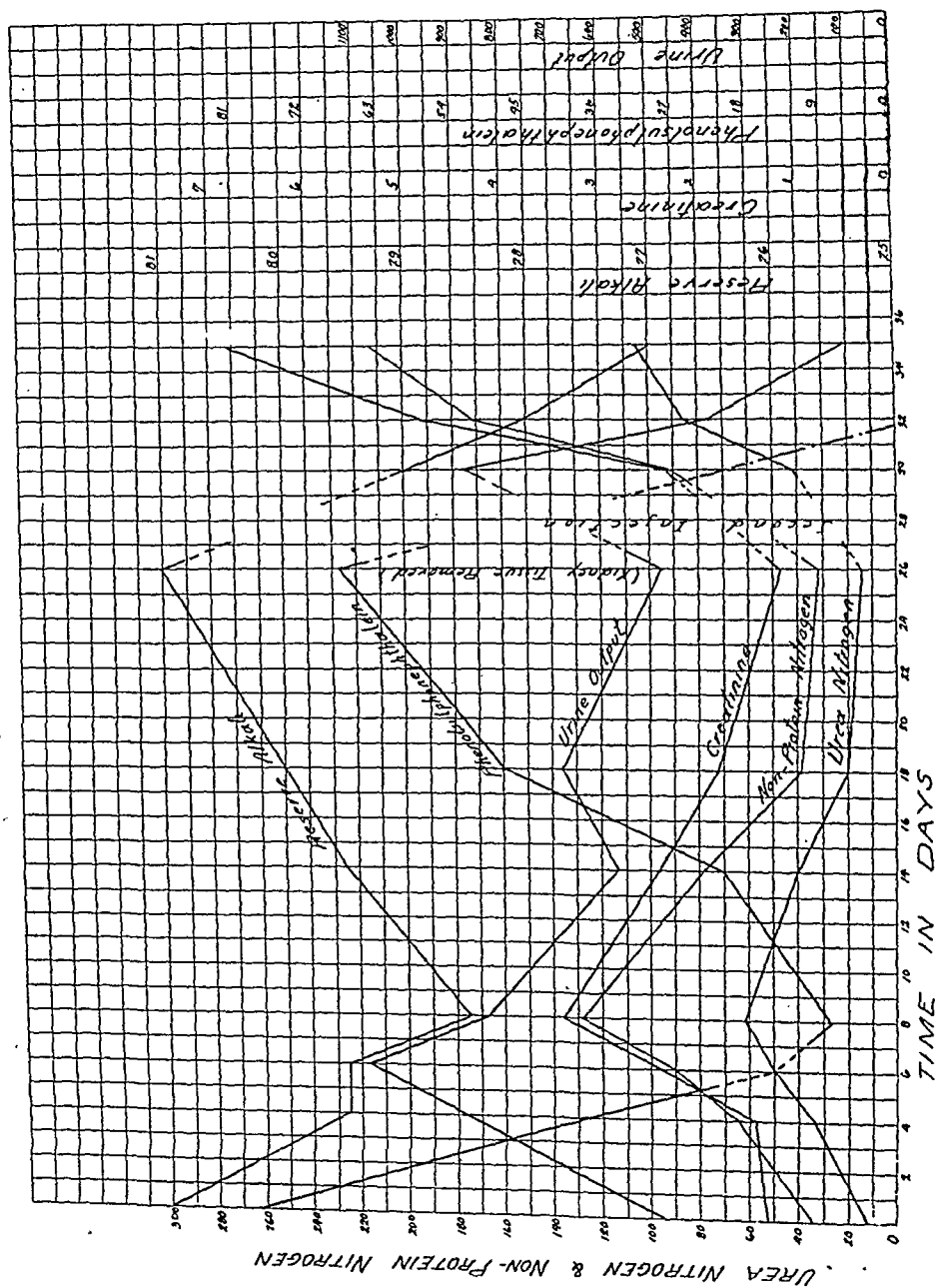


CHART VII

flattened, atypical type of epithelium, which gives to such kidneys their resistance to uranium. In such areas there was no evidence of degeneration from the second injection of uranium, which in certain of the dogs was given in twice the original amount. In other tubules there was both evidence of cell degeneration of epithelium normal for the convoluted tubules and repair by the flattened type of cell, and, last, there were tubules in which there





The evidence presented in this lecture, which largely concerns itself with an analysis of the functional value in terms of secretion of the epithelium of the proximal convoluted tubules, is lacking in absolute proof, for these structures have not been separated from other interrelated structures, and as such their functional values determined. For the higher animals this probably cannot be completely accomplished. In such animals the exact function of a particulate but intimately related structure can only be ascertained by finally gaining an understanding of such structures in terms of their functional evolution. When this type of research is welded together in a functional whole renal function will be understood in the higher animals just as similar studies of structural evolution have given us an understanding of its highest complexity in man.

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## WATERMELON-SEED EXTRACT IN THE TREATMENT OF HYPERTENSION.

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IN 1926, Barksdale<sup>1</sup> investigating extracts of the seed of the watermelon (*Cucurbita citrullus*) isolated a physiologically active glucoside-saponin which he named "cucurbocitrin." The main effect of cucurbocitrin in normal dogs and man is that of lowering the arterial tension. Direct microscopic measurements on capillaries of the frog showed that their diameter was more than doubled after administration of the drug. Similarly studies with the Danzer-Hooker microcapillary tonometer in man revealed a lowering of the capillary pressure from an average of 16 mm. before to an average of 9 mm. after the administration of this substance, thus strongly suggesting that reduction in the blood pressure is brought about by capillary dilatation. The possibility that the action of cucurbocitrin is due to cardiac depression was ruled out by direct perfusion experiments with the frog's heart.

Cucurbocitrin is active when given by mouth and its use is perfectly safe. Twenty milligrams of it produces definite lowering of the blood pressure in normal individuals, and as much as 300 mg. have been given in a single dose without ill effects. The lethal dose for rabbits is 200 mg. per kilo of body weight. For details of the chemistry and pharmacology of cucurbocitrin the reader is referred to the original article of Barksdale.<sup>1</sup>

Clinically, cucurbocitrin was tried by Barksdale with success in 10 cases of hypertension due to tuberculous nephritis, but his results with high blood pressure in several arteriosclerotic patients were unsatisfactory. Wilkinson<sup>2</sup> reported the use of this drug in 68 cases of "hypertensive cardiovascular disease" obtained in coöperation with some twenty physicians. In this series 56 out of the 68 patients "showed a sufficient reduction in the arterial tension to be of clinical importance and the relief of symptoms was frequently out of proportion to the drop in pressure." The author feels that cucurbocitrin is more efficacious in hypertension associated with the menopause, senility and obesity.

With this information at hand it seemed worth while to subject to cucurbocitrin therapy a thoroughly studied and well-controlled

group of clinical patients with hypertension, in an attempt to determine, if possible, the type or types of hypertension responding favorably to this treatment. Our second aim in undertaking this work was a comparison of the results obtained by cucurbititrin with those achieved with liver-extract therapy.

The present study was made possible through the courtesy of Dr. I. S. Barksdale and the Table Rock Laboratories of Greenville, South Carolina, by whom the drug was supplied.

**Selection and Examination of Patients.** We realized the obstacles encountered in any experiment involving deductions from a therapeutic procedure and the particular difficulties involved in dealing with hypertension. For this reason, the work was carried out as much as possible in the out-patient department where the patients' habits and environment could be left undisturbed, thus eliminating the most important factor of uncertainty which enters into the appraisal of results obtained in the treatment of hypertension in hospitalized individuals. In all but four cases, the treatment was carried out entirely in the Clinic. Moreover, two of the three hospital cases in which reduction of blood pressure was produced were followed later in the out-patient department. In the hospitalized patients, cucurbititrin therapy was started only after the blood pressure had become stabilized in the new environment, the patients spending from seven to thirty-three days in bed before the beginning of treatment.

No selection of cases for cucurbititrin medication was attempted, but a number of patients whose hypertension had failed to yield to liver-extract therapy were put on cucurbititrin.

In every case, a complete history was taken and a general physical examination done with special attention to features indicative of involvement of the kidneys, heart and bloodvessels. The laboratory investigation included a complete analysis of urine, the phenolsulphonaphthalein test, the Mosenthal test, and the blood Wassermann test. All reported cases had a negative Wassermann reaction. In addition, blood-urea and nonprotein-nitrogen determinations were done in 23 cases, but later discontinued when a preliminary analysis disclosed that they had no bearing on the success or failure of cucurbititrin therapy. Teleroentgenograms of the heart and electrocardiograms were taken, as indicated.

The majority of patients before receiving cucurbititrin had gone through a period of treatment by dietetic measures (especially withdrawal of salt), and sedatives (mostly luminal) without much success. It goes without saying that no other treatment having any possible influence on blood pressure was given to the reported cases during the period of cucurbititrin administration.

**Methods of Observation and Treatment with Cucurbititrin.** Blood-pressure measurements were carried out in the morning with the same sphygmomanometer applied to the right arm of patients

who had rested in the prone position for ten to fifteen minutes. The auscultatory method was used.

In determining the average blood pressure before treatment, at least several measurements were taken on different days and in the majority of cases the patients had been under observation for several months and often years prior to receiving cucurbititrin. The average blood pressure following treatment was recorded for the entire period if the latter was less than one month and for the last month if it extended over several months, even if intermediate months showed a lower average.

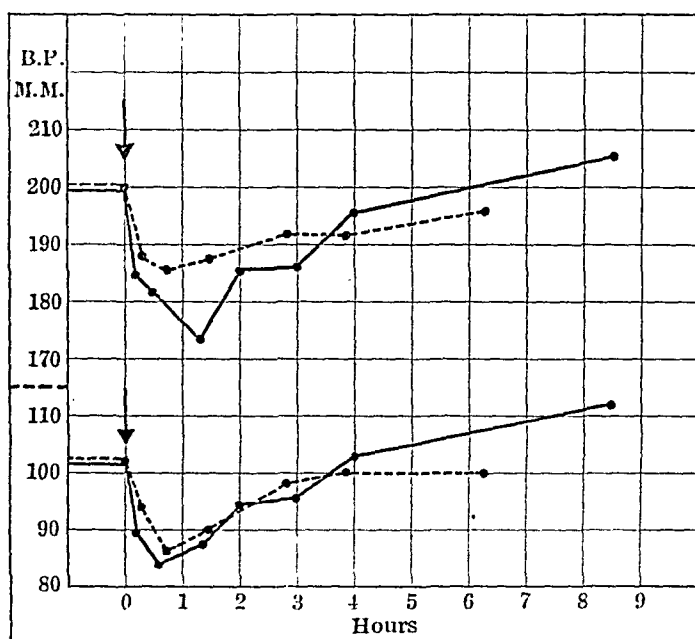


CHART I.—Chart showing immediate effects of cucurbititrin on the systolic and diastolic blood pressure. The broken line indicates the effects of 100 mg. and the unbroken line those of 150 mg. of cucurbititrin. Arrows indicate when cucurbititrin was given by mouth.

In the case of patients who had received liver extract before cucurbititrin, the latter was credited with reduction of hypertension only in comparison with the average blood-pressure level while receiving liver-extract injections unless at least three months had elapsed since the last injection, a period which, as experience has shown, is sufficient to exhaust the effect of liver extract in a great majority of even the most favorable cases.

Cucurbititrin was given by mouth in capsules containing 50 mg. of the glucoside. After some preliminary experimentation an optimum dosage of one capsule three times a day was arrived at and used in most cases. To several patients 100 mg. and to one patient 150 mg. of the drug was prescribed three times a day. After two weeks of treatment it usually became apparent whether continuation of medication was indicated.

**Results of Cucurbocitrin Therapy.** I. *Immediate Effects:* Following a single oral dose of cucurbocitrin there is usually in hypertension cases a fall of the systolic and diastolic pressure beginning about fifteen minutes after the administration of the drug. The degree of reduction of blood pressure is more or less in proportion to the dose in the same patient, as can be seen from Charts I and II. The same is true in regard to the duration of the lowering of arterial tension following a single dose. It is of interest that patients often spontaneously reported diminution of symptoms even after one dose of the drug.

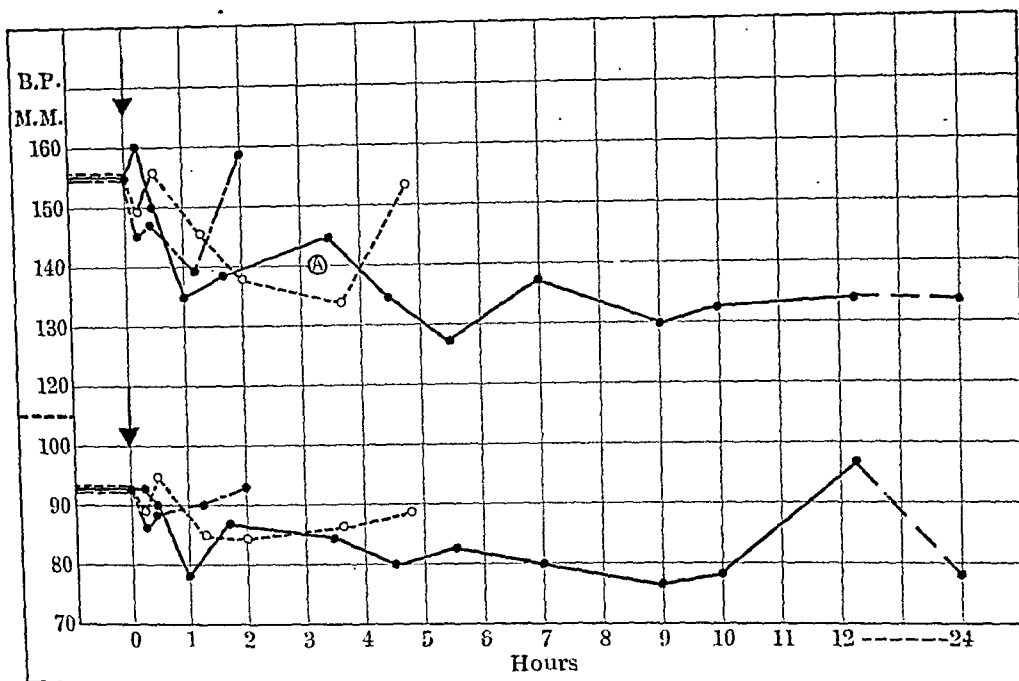


CHART II.—Chart showing immediate effects of cucurbocitrin on the systolic and diastolic blood pressure of another patient. The irregularly broken line shows blood pressure curves after 50 mg., the regularly broken line after 100 mg., and the unbroken line after 150 mg. of cucurbocitrin orally. Arrows indicate when cucurbocitrin was given. A, patient had lunch.

II. *Results of Prolonged Cucurbocitrin Administration.* In favorable cases, prolonged administration of cucurbocitrin brings about lasting reduction of hypertension which almost invariably is accompanied by symptomatic improvement of the patient. In Chart III are given blood-pressure curves from two cases of hypertension in which the latter was markedly reduced in the course of cucurbocitrin therapy. Altogether 40 cases of hypertension were given cucurbocitrin and the important clinical findings in each case summarized in Table I. Twenty-one of the 40 patients received injections of liver extract, 14 before and 7 after a period of cucurbocitrin administration and a comparison of the action of these two therapeutic remedies will be made at the end of this report. The average time of treat-

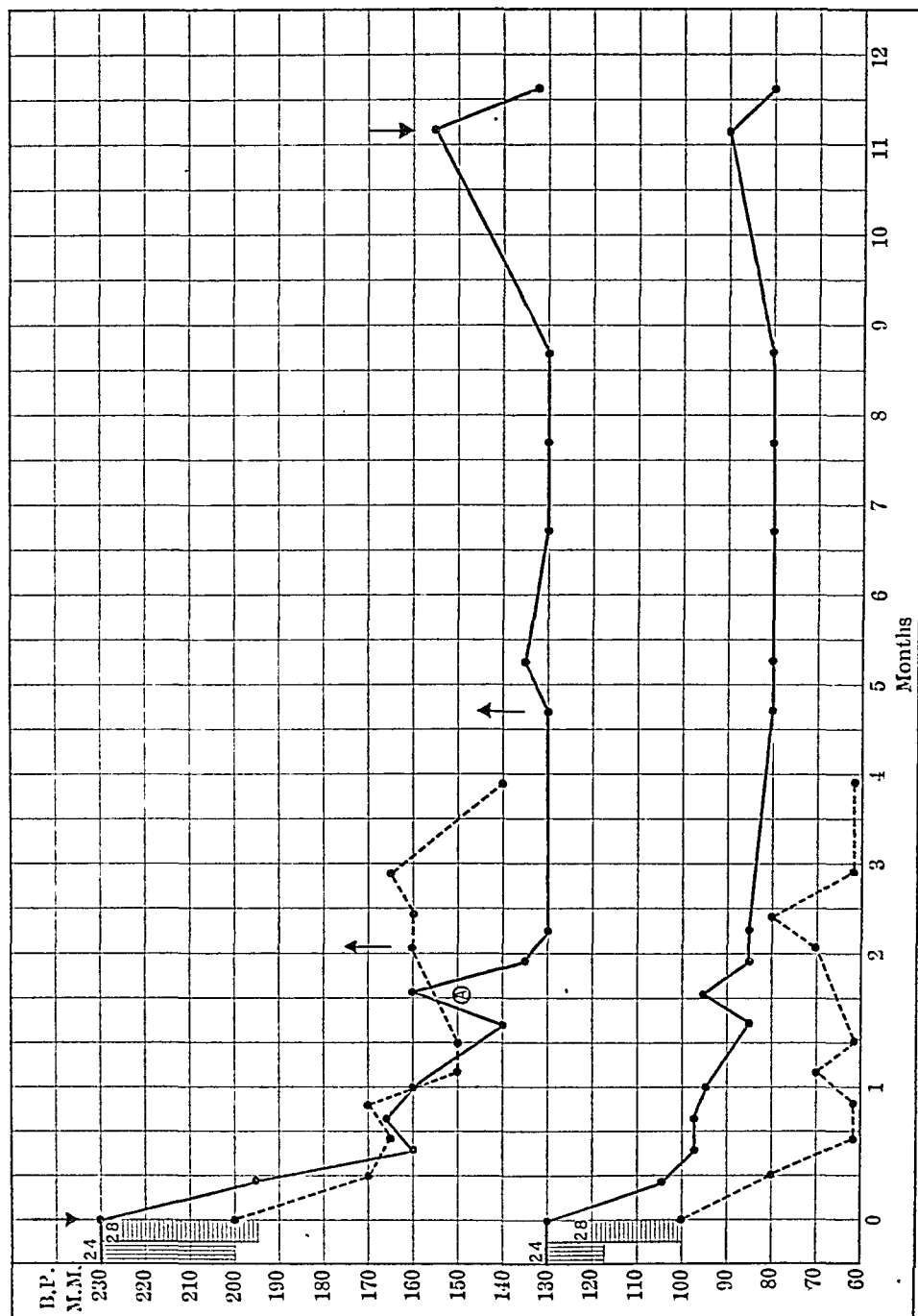


CHART III.—Chart showing prolonged lowering of the systolic and diastolic blood pressure in 2 hypertension cases (Nos. 24 and 28) who reacted favorably to cucurbiticin therapy. Rectangles indicate the range of fluctuations of the blood pressure prior to cucurbiticin administration. Arrows pointing down indicate the beginning of treatment. Arrows pointing up show discontinuation of cucurbiticin. A, patient had respiratory infection with exacerbation of chronic cholecystitis.

ment with cucurbiticin for 35 cases who responded by reduction of hypertension or improvement of symptoms, or both, was one hundred days. The average duration of cucurbiticin therapy in 5 patients who failed to respond to treatment was thirty-eight days.

*Lowering of the Average Systolic Blood Pressure.* Lowering by 10 mm. or more took place in 29 out of 40 cases, or in 73 per cent of

all cases. The average lowering of systolic pressure in all cases who responded in this way was 22 mm. Since the majority of patients who received liver extract first were taken off liver-extract injections and put on cucurbititrin because they did not respond satisfactorily to the former method of treatment, a certain adverse selection of intractable cases crept in. It is, therefore, of interest that the average reduction of the systolic blood pressure of the unselected group in which patients received cucurbititrin first was 29 mm. Reduction of the diastolic pressure was usually in proportion to that of the systolic and the average for all cases amounted to 15 mm.

The greatest total fall in blood pressure in any one case was 81/43 mm. (from 211/123 to 130/80). The most marked reduction of blood pressure produced in a short period of time was 35/25 mm. in the first and in addition 35/7 mm. in the second week of cucurbititrin administration in Case 26.

*Symptomatic Relief.* This was reported in 32 out of 39 cases with symptoms referable to hypertension or in 82 per cent of all cases. Of these cases 3 (or 9 per cent) reported complete relief of their symptoms; 18 (or 56 per cent) were markedly improved; and 11 (or 34 per cent) were partially relieved.

The symptoms given by patients in order of their incidence and those that were completely or markedly improved are given in Table II. The most frequent symptoms were: headaches, dyspnea, dizziness,<sup>a</sup> palpitation, edema, tinnitus and visual disturbances. The complaints relieved in the largest per cent of their occurrence were: precordial pain, insomnia, dyspnea, palpitation, nervousness and headaches.

Partially relieved symptoms were omitted from this Table owing to a desire to exclude any possible psychic effects of the treatment.

**Discussion.** A reduction in blood pressure of 10 mm. or more was accompanied by symptomatic improvement in all but three cases and every patient whose blood pressure was reduced by 40 mm. or more was completely or markedly relieved of symptoms. On the other hand, even marked subjective improvement was at times reported without a corresponding lowering of hypertension.

Therefore, as in our preceding paper on the use of liver extract in the treatment of hypertension, it was found expedient to analyze separately the possible factors making for reduction in blood pressure and for symptomatic relief. In this manner, our successes and failures in these two respects are analyzed below from the standpoint of age, sex, degree and duration of hypertension, body weight, renal damage, cardiovascular changes, and the menopause in the female. A minimum reduction in the systolic pressure of 10 mm. and partial relief of symptoms were adopted as criteria of success in the following analysis, but the grouping of clinical data on the basis of a minimum reduction of 20 mm. and complete or marked symptomatic improvement was essentially similar.



TABLE I.—CLINICAL DATA AND EFFECTS OF CUCURBOCITRIN

Case.	Age. Sex.	Duration of hypertension.	Deviation from normal weight in per cent.	Menstrual status.	Symptoms.	Physical findings.		Blood Pressure.			
						Cardiac signs.	Arterio-sclerosis.	Average before treatment.	Average after liver extract.	Average after cucurbitr.	Average reduction with cucurbitr.
1	48 F	1 yr.	13—	Hysterectomy 5 yrs. ago	Headache, nervousness, fatigue, dizziness; palpitation	Slight cardiac enlargement	Mod.	220 115	199 103	182 92	17 11
2	62 F	5 yrs.	2+	Menopause 12 yrs. ago	Headaches, dyspnea	Slight ankle edema; systolic murmur at apex	Mod.	196 91	199 89	180 96	19 7
3	49 M	2 yrs.	1+	...	Apoplexy 1 and 2 yrs. ago; fatigue	Systolic murmur at apex	Mod.	173 104	177 102	160 90	17 12
4	50 F	15 yrs.	14—	Menopausal symp. for one year	Headaches, dyspnea, palpitation, transitory blindness; hot flushes	Systolic murmur at apex. Ecg. S2 slightly slurred	Mod.	194 110	191 113	190 121	..
5	59 F	3 yrs.	6—	Menopause 14 yrs. ago	Headaches, dizziness, fatigue, nervousness, visual disturbances, speech difficulties, lapses of memory, numbness of extremities, right facial weakness	Slight cardiac enlargement; systolic murmur at apex; Ecg. myocardial damage	Mod.	258 136	255 123	250 130	..
6	49 F	4 mos.	25+	Menopause 4 yrs. ago. Rare hot flushes	Severe daily headaches	Systolic murmur at base	Mod.	229 140	203 115	215 145	14 5
7	50 F	3 yrs.	13—	CTA regular	Constant headaches, nervousness, lapses of memory, tinnitus, difficulties in walking, inability to dress	Systolic murmur at apex	Marked	190 106	193 102	175 98	18 4
8	41 F	3 yrs.	10+	CTA regular	Severe headaches, nervousness, tinnitus, palpitation, dizziness, sleeplessness.	Moderate cardiac enlargement	None	218 130	188 114	201 119	17 11
9	66 M	3 yrs.	3+	....	Dyspnea, headaches, dizziness, paralysis of right leg	Systolic murmur at base	Marked	217 107	219 100	210 70	..
10	28 F	2 yrs.	10—	CTA regular	None	None	None	185 105	197 118	190 120	..
11	53 F	4 yrs.	5+	Menopause 8 yrs. ago	Headache, palpitation, dizziness, dyspnea, precordial pain after heavy meals	Slight cardiac enlargement, systolic murmur at base, Ecg. right B. B. block; Roentgen ray aortic heart	Mod.	227 124	230 131	215 115	15 16
12	45 M	4 yrs.	21—	....	Headaches, dyspnea, epistaxis, right facial paralysis	Marked enlargement; loud A2; Roentgen ray aortic heart; Ecg. right B. B. block	Mod.	217 142	225 151	202 158	23 7
13	38 F	5 yrs.	9+	CTA regular	Headaches, dyspnea, precordial pain, palpitation, dizziness, blurring of vision	Slight enlargement; loud A2; systolic murmur at apex. Roentgen ray slight enlargement and hypertrophy	Mod.	250 139	215 106	207 105	43 34
14	54 M	7 yrs.	2+	....	Severe dizziness, epistaxis, slurring of speech, confusion, weakness, "stroke" affecting legs 1 yr. ago	Enlargement to left, loud A2; sounds of poor quality. Ankle edema; Ecg. partial A-V block; left preponderance	Marked	210 118	192 110	174 96	18 14
15	69 M	3 yrs.	2+	....	Severe daily headaches, dyspnea, fatigue, blurring of vision	Cardiac enlargement; Roentgen ray aortic heart; systolic murmur at base	Marked	263 144	255 137	238 123	..
16	51 M	6 mos.	20—	....	Headaches, dizziness, blurring of vision	Moderate cardiac enlargement; systolic murmur at apex; Ecg. myocardial damage	Marked	193 127	178 110	174 111	15 17
17	48 M	1 yr.	20+	....	Headaches, dyspnea, palpitation, left hemiplegia	Slight ankle edema	Mod.	177 112	164 105	169 112	13 7
18	56 F	11 mos.	17—	Menopause 5 yrs. ago	Headaches, palpitation, fatigue, mental depression	Marked enlargement; loud A2, systolic murmur at apex; Roentgen ray hypertrophy and enlargement to left. Ankle edema	Mod.	235 140	228 134	227 135	..
19	46 F	2 yrs.	8+	CTA regular	Severe headaches, tinnitus, fatigue	Systolic murmur at apex	Mod.	197 95	198 75	194 74	..
20	43 F	6 yrs.	5+	CTA regular	Headaches, dyspnea, palpitation, nervousness	Slight enlargement; loud A2; systolic murmur at apex. Slight ankle edema; Roentgen ray slight enlargement	Mod.	249 133	233 113	230 124	16 20

IN A GROUP OF 40 HYPERTENSION CASES.

Laboratory findings.						Symptomatic relief from cucurbitacin.	Symptomatic relief from liver extract.	Duration of cucurbitacin therapy, days.	Previous treatment.	Remarks.
Uring.		Mosenthal test.		Phthalein test.	Blood chemistry mg. per 100 cc.					
Albumin.	Casts.	Nocturnal poly-uria.	Fixation of specific gravity.							
0	0	0	0	80	Urea N. 20.1	Comp.	Comp.	90	None	With double dose B. P. 170/97; 2 mos. without drug B. P. 190/80; 3 mos. without drug B. P. 220/80. Headache.  3 weeks without drug, B. P. 182/100.
0	0	0	0	51	Urea N. 16.8	Marked	Mod.	250	Low salt, pyramidon	
0	0	0	0	30	Urea N. 13.1	Marked	Marked	293	Low salt, low protein Luminal, Ki	
FPT	0	0	7 pts.	70	Urea N. 16.8	None	None	32	Low salt, low protein and fluids, luminal	
T.	Rare hyaline	0	5 pts.	32.5	Urea N. 21 N.P.N. 35.3	Mod.	None	43	Low salt, luminal, rest, Ki, ovarian extract	Roentgen-ray aortitis.
S. T.	0	+	6 pts.	55	N.P.N. 50	Marked	Marked	94	Low salt	1 mo. without drug no relapse.
F. P.T.	0	0	0	30	....	Marked	Marked	173	None	1 mo. without drug B. P. 185/105.
F. P. T.	0	+	4 pts.	50	....	Marked	Mod.	125	Low salt, low caloric, luminal	1 mo. without drug, headaches.
0	0	0	0	40	....	None	None	34	Low salt, luminal, allonal, Ki	
0	0	0	0	100	....	.....	.....	72	Low salt	
S.T.	0	0	0	55	....	Marked	Marked	157	Luminal	2 mos. without drug B. P. 250/130. Roentgen ray sclerosis of arch.
H.T.	Gran. cell and hyaline	+	0	30	Urea N. 25.2 N.P.N. 36.6	Marked	None	127	Low salt, low protein. Luminal	Rest in bed 8 days before treatment. With double and triple dose no greater effect; 1 mo. without drug B. P. 245/160. Roentgen ray enlarged and sclerotic arch.
0	0	0	7 pts.	70	....	Marked	Marked	180	None	Drug stopped twice for 6 weeks; symptoms recurred both times, B. P. 218/112 second time. Roentgen ray sclerosis of arch.
F. P. T.	Many hyalin	0	5 pts.	25	Urea N. 14.9 N.P.N. 28.5	None	None	54	Low salt, low protein bed rest. Catharsis	1 week without drug B. P. 190/110. Roentgen ray marked sclerosis of arch.
F. P.T.	Occ. hyalin and cell	+	0	32.5	Urea N. 17.3	Marked	Marked	87	Low salt, low protein, allonal, pyramidon q. 4 hrs.	Roentgen ray aortitis.
H. T.	Many hyalin	0	0	75	Urea N. 14	Mod.	Marked	14	Low salt, limited fluids, luminal, Ki	Roentgen ray sclerosis of arch.
F.P.T.	0	0	0	55	....	Marked	Marked	72	Luminal	1 week without drug, B. P. 175/120. Headaches.
H.T.	0	+	0	55	Urea N. 14.2 N.P.N. 38.4	None	None	28	Low salt, low protein. Rest, luminal nitrates	Roentgen ray sclerosis of arch.
F.P.T.	0	0	3 pts.	60	....	Mod.	None	74	None	
F.T.	0	+	0	70	N.P.N. 44.4	Mod.	Mod.	51	Low salt, low protein, luminal, Ki	2 weeks without drug B. P. 260/130.

TABLE 1.—CLINICAL DATA AND EFFECTS OF CUCURBOCITRIN

Case.	Age.	Sex.	Duration of hypertension.	Deviation from normal weight in per cent.	Menstrual status.	Symptoms.	Physical findings.		Blood Pressure.			
							Cardiac signs.	Arterio-sclerosis.	Average before treatment.	Average after liver extract.	Average after cucurbitrin.	Average reduction with cucurbitrin.
21	57	M	6 wks.	6+	....	Headaches, palpitation on exertion, epistaxis, parathesias of extremities, lapses of memory	Slight enlargement; sounds indistinct	Marked	176 106	163 108	173 103	13 2
22	57	F	6½ yrs.	8—	Menopause 4 yrs. ago	Headaches, palpitation, dyspnea	Slight cardiac enlargement; loud A2; systolic murmur at apex	Mod.	197 108	153 92	...	44 16
23	53	M	7 mos.	15—	....	Dizziness, unsteady gait	Slight cardiac enlargement; loud A2; diastolic murmur at base	Marked	240 130	217 117	...	23 13
24	50	F	8 yrs.	2—	Menopausal symptoms, hot flushes	Headaches, dizziness, insomnia	Loud A2, ankle edema	Mod.	205 103	160 70	...	45 33
25	63	F	5 yrs.	12+	Menopause 20 yrs. ago	Dyspnea; occasional cardiac pain, pain in eyes	Slight enlargement, systolic murmur at apex, ankle edema	Mod.	160 85	153 75	...	...
26	56	F	2½ mos.	13—	Menopause, 8 yrs. ago	Headaches, dyspnea	None	None	211 123	130 80	...	61 43
27	41	M	5 yrs.	7—	....	Headaches, dyspnea, palpitation, dizziness, insomnia, tinnitus, parathesias of extremities	None	None	171 90	137 79	...	34 11
28	77	M	2 mos.	2—	....	Nervousness, fullness in head	Slight enlargement; loud A2	Mod.	196 105	153 67	...	43 38
29	38	F	1 mo.	25—	CTA regular	Severe headaches, dizziness, tinnitus	None	None	179 110	148 90	..	31 20
30	55	F	2 yrs.	15+	Menopause, 10 yrs. ago	Palpitation, dyspnea, tinnitus, nervousness	Enlargement to left, extrasystole; loud A2. Systolic murmur at apex. Ecg. shows left preponderance	Mod.	190 77	160 56	..	30 21
31	57	M	6 yrs.	7+	....	Precordial pain, dizziness, dyspnea, headaches	Marked enlargement, loud A2, systolic murmur at apex; Ecg. neg.	Mod.	217 112	195 77	...	22 35
32	42	F	8 yrs.	4—	Menopausal symptoms; irregular flow and hot flushes	Headaches, dyspnea, tinnitus	Moderate enlargement to the left. Systolic murmur at apex; Ecg. shows myocardial damage, slight ankle edema	Marked	220 128	192 123	...	28 5
33	62	F	15 yrs.	12—	Menopause, 17 yrs. ago	Dizziness, visual disturbances, tinnitus, impairment of memory, nervousness, speech difficulties, numbness of extremities, weakness	Slight enlargement, loud A2, systolic murmur at apex, Ecg. normal	Mod.	188 102	188 101	...	..
34	53	F	7 yrs.	1+	Menopause 7 yrs. ago	Headaches, dyspnea, visual disturbances	Slight enlargement, loud A2, systolic murmur at apex	Mod.	188 95	177 66	...	11 31
35	55	F	20 yrs.	1+	Menopause 2 yrs. ago	Headaches, dyspnea, palpitation, tinnitus, tachycardia, dizziness	Slight enlargement, systolic murmur at apex; Ecg. shows myocardial damage	Mod.	203 97	162 82	...	41 15
36	38	F	3 yrs.	8—	Menopausal symptoms	Headaches, dyspnea	Loud A2, systolic murmur at apex, ankle edema	None	231 129	221 140	...	10 11
37	56	F	2 yrs.	30+	Menopause 18 yrs. ago	Headaches, dyspnea, dizziness, continuous precordial pain	Moderate enlargement, loud A2, systolic murmur at apex, extrasystoles, ankle edema; Ecg. myocardial damage	Marked	212 117	200 119	...	12 2
38	60	F	2 yrs.	27+	Menopause 24 yrs. ago	Headaches, loss of memory	Loud A2	None	208 117	192 104	...	16 13
39	49	F	3 wks.	56+	Menopausal symptoms for 4 yrs.	Paresthesias (numbness) of left foot	Marked enlargement	Mod.	186 108	186 113	...	..
40	49	M	2 yrs.	3—	....	Dyspnea, palpitation	Moderate enlargement, loud A2, systolic murmur at apex, ankle edema, Ecg. shows myocardial damage	Slight	196 123	195 114	...	..

# IN A GROUP OF 40 HYPERTENSION CASES—(Continued).

Laboratory findings.						Symptomatic relief from cucurbitacin.	Symptomatic relief from liver extract.	Duration of cucurbitacin therapy, days.	Previous treatment.	Remarks.
Urine.		Mosenthal test.		Phthalein test.	Blood chemistry mg. per 100 cc.					
Albumin.	Casts.	Nocturnal polyuria.	Fixation of specific gravity.							
F.P.T.	0	0	0	60	....	Mod.	Marked	72	None	With double dose no greater effects.
0	Few hyalin	0	0	50	Urea N. 8.4	Marked	.....	105	Rest	2½ mos. without drug, B. P. 180/110.
0	0	0	0	55	....	None	.....	52	Luminal	1 week without drug, no relapse.
F.T.	0	0	5 pts.	55	....	Marked	.....	164	Low salt, low protein; limited fluids, luminal, rest, ovarian extr. pyramidon	2 weeks without drug, no relapse; 6 weeks without drug, B. P. 195/103.
F.T.	0	0	0	55	....	Marked	.....	78	Low salt, low protein; limited fluids, luminal, Ki ovarian extract	1 mo. without drug, no relapse.
F.T.	0	+	0	90	Urea N. 12.1	Comp.	.....	313	Low salt diet	5 mos. without drug, no relapse; 7½ mos. without drug, B. P. 155/90 2 wks. after cucurbitacin, B. P. again 132/80.
0	0	+	0	65	....	Mod.	.....	120	Low salt, low protein; luminal, Ki	
0	0	0	0	35	....	Comp.	.....	120	Low salt, low protein, and luminal, Ki, pyramidon	1 mo. without drug, B. P. 165/60.
0	0	0	5 pts.	70	....	Mod.	.....	137	Luminal	3 mos. without drug, B. P. 168/100.
H.T.	Occ. hyalin	0	0	60	....	Marked	.....	93	Low salt, protein and caloric diet	1 mo. without drug, no relapse; Roentgen ray evidence of considerable sclerosis of arch.
0	0	0	0	65	....	Mod.	.....	21	Low salt, Ki; nitroglycerin, luminal, digitalis	Roentgen ray sclerosis of arch.
T.	Occ. cellular	0	5 pts.	20	N.P.N. 42.8	Mod.	.....	18	Low salt, low protein, luminal	Hospital patient, in bed 18 days before treatment. Roentgen ray sclerosis of arch.
F.P.T.	Occ. granular	..	..	42	Urea N. 15.6 N.P.N. 46.1	None	.....	21	Luminal, ovarian extract	Hospital patient, rest in bed 33 days before treatment.
F.P.T.	Occ. granular	+	0	70	....	Marked	.....	142	Low salt, low protein; ovarian extract	1 mo. without drug, B. P. 205/80 and headaches.
T.	0	..	..	59	....	Marked	.....	54	Low salt, low protein	Double dose of cucurbitacin produced no greater results. Hospital pt. in bed 7 days before R.
F.T.	0	0	0	65	Urea N. 18.8 N.P.N. 30.1	None	.....	18	Low salt, low protein, KI, luminal	Double dose of cucurbitacin lowered B. P. by another 26 mm.
F.T.	0	..	..	..	....	Marked	.....	100	Luminal, digitalis, nitroglycerin, bed, rest	Double dose produced no further improvement. Roentgen ray sclerosis of arch.
0	0	0	0	50	....	Mod.	.....	40	None	No greater results with double dose.
F.T.	0	..	..	..	....	Marked	.....	19	Rest	
T.	0	0	0	60	....	Mod.	.....	26	Luminal, digitalis	

TABLE II.—SYMPTOMS ASSOCIATED WITH HYPERTENSION IN OUR SERIES AND THOSE COMPLETELY OR MARKEDLY RELIEVED BY CUCURBOCITRIN THERAPY.

Symptoms.	No. of cases.	Per cent.	No. of cases improved.	Per cent improved.
Headaches . . . . .	31	80	17	55
Dyspnea . . . . .	21	55	13	62
Dizziness . . . . .	16	41	7	44
Palpitation . . . . .	14	38	8	57
Edema of legs . . . . .	9	24	4	44
Tinnitus . . . . .	9	24	4	44
Visual disturbances . . . . .	9	24	4	44
Fatigue . . . . .	8	20	4	50
Nervousness . . . . .	7	19	4	57
Impairment of memory . . . . .	6	16	1	17
Precordial pain . . . . .	5	13	4	80
Numbness of extremities . . . . .	5	13	1	20
Unsteadiness of gait . . . . .	4	10	1	25
Insomnia . . . . .	3	8	2	67
Epistaxis . . . . .	3	8	1	33
Speech disturbances . . . . .	3	8		
Mental depression . . . . .	1	3		

The systematized data are presented in the accompanying tables which are largely self-explanatory.

*Age.* This according to Table III, seems to play some rôle in determining the success of cucurbitrin in lowering high blood pressure, the successful cases being on the average six years younger than the unsuccessful ones. Also, the average age of patients who failed to get symptomatic relief is five and a half years higher than that of the group composed of cases who did.

*Sex.* Sex, on the contrary, had no appreciable influence on the outcome of treatment either as to reduction of hypertension or symptomatic benefits.

*The Degree of Hypertension.* This proved to be of no great consequence so far as the results of cucurbitrin therapy are concerned.

*The Duration of Hypertension.* As calculated from the time of detection by instrumental means this appears to have a definite prognostic significance in regard to the symptomatic results of cucurbitrin therapy. From the same table we see that patients who failed to obtain improvement of their symptoms were known to have had hypertension on the average almost twice as long as the successful cases. This does not hold true when applied to the prospects of blood pressure reduction.

*Influence of Body Weight on the Outcome of Treatment.* The patients were weighed with their clothes on and their "normal" (not ideal) weight calculated on the basis of sex, height (with shoes), and age, according to tables based on data obtained from the examination of 358,323 American men and women.<sup>3</sup> As can be seen from Table III, the difference in the average weight of the four groups is insignificant, especially in view of the fact that

insurance experts allow 20 per cent above or below as a safe variation from the supposedly healthy average normal weight. Approaching the question of body weight from another angle by segregation of all patients who are 20 per cent or more overweight, we again failed to see any influence of body weight on tractability of hypertension.

*Bearing of Kidney Involvement on Results of Treatment.* Only six patients in this series were free of demonstrable kidney damage and these six did not respond in a uniform way to cucurbititrin administration. The outcome of the various kidney tests is correlated in Table IV with the clinical results.

*Urinary Findings.* A negative urine analysis was found twice as often in patients who responded by lowering of their blood pressure than in those whose blood-pressure remained unchanged. On the other hand, the percentage of negative urinary findings was practically the same in the group of patients showing symptomatic relief as well as in the unrelieved group. Of the individual abnormal constituents of the urine, albumin was found more frequently in patients whose blood pressure remained unchanged, and also somewhat more often in patients who reported symptomatic improvement. On the other hand, casts were found with equal frequency in all groups.

*Phenolsulphonephthalein Excretion Test.* The success of cucurbititrin therapy in hypertension is apparently not influenced by the power of the kidneys to excrete dyes, as shown by the average phthalein excretion values.

*Blood-urea Nitrogen and Total Nonprotein-nitrogen Determinations.* Blood chemistry investigations were carried out in 17 of the earlier cases, but later were discontinued after an analysis of the results showed these had no bearing on the success or failure of cucurbititrin therapy.

*Mosenthal Test.* More negative Mosenthal tests were found among the patients whose blood pressure was reduced by cucurbititrin. Fixation of specific gravity was found somewhat more frequently among the two failure groups. On the other hand, nocturnal polyuria occurred more often among patients who claimed relief from cucurbititrin medication. However, in no two groups were the differences in the results of the Mosenthal test of sufficient magnitude to permit us to draw any definite conclusions in regard to the possible bearing of vascular nephritis on the success of cucurbititrin treatment.

*Results of Treatment in the Light of Cardiovascular Damage.* Quantitative appraisal of organic disease of the heart and blood-vessels is so difficult that only a rough distinction between "marked" and "moderate" involvement of either is attempted below.

*Cardiac Damage.* Data on which the degree of cardiac involvement was judged are given in Table I. From a percentage analysis of the amount of cardiac involvement in the four groups in Table V,

TABLE III.—INFLUENCE OF AGE, SEX, HEIGHT OF BLOOD PRESSURE, DURATION OF HYPERTENSION, AND BODY WEIGHT  
ON RESULTS OF TREATMENT WITH CUCURBOCITRIN.

Group of patients.	Average age, years.	Sex.				Average blood pressure before treatment.		Duration of hypertension, years.	Average weight above or below normal, per cent.
		Males.		Females.		Systolic.	Diastolic.		
		Cases.	Per cent.	Cases.	Per cent.				
Blood pressure reduced 10 mm. or more	50.5	9	69	20	74	206	115	4.7	0.9 +
Blood pressure unchanged	56.6	4	31	7	26	208	110	4.3	1.9 +
Symptomatic relief obtained	50.2	10	77	22	85	205	113	3.6	3.2 +
No symptomatic relief	55.6	3	23	4	15	214	119	6.4	6.4 —

TABLE IV.—BEARING OF KIDNEY INVOLVEMENT IN HYPERTENSION ON THE SUCCESS OF CUCURBOCITRIN THERAPY.

Group of patients.	Urinary findings.						Average phenol-sulphone-phthalein excretion in per cent.	Average blood-urea nitrogen level in mg. per 100 cc.	Mosenthal test.					
	Albumin.		Casts.		Negative.				Nocturnal polyuria.		Fixation of specific gravity.		Negative.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.			Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Blood pressure reduced 10 mm. or more . . . . .	18	62	7	24	10	34	55.7	15.9	7	26	7	26	16	59
Blood pressure unchanged . . . . .	9	82	3	27	2	18	54.5	17.0	2	22	3	33	4	44
Symptomatic relief obtained . . . . .	22	69	8	25	9	28	55.1	16.4	8	28	8	28	15	52
No symptomatic relief . . . . .	4	57	2	29	2	29	49.5	16.0	1	17	2	33	3	50

it appears that the degree of involvement of the heart when present has no bearing on the success of cucurbocitrin therapy. On the other hand, the absence of cardiac disease is a favorable factor inasmuch as only one patient without demonstrable involvement of the heart failed to obtain lowering of the blood pressure and the symptomatic success of the treatment was universal in all such cases.

*Arteriosclerosis.* Hardening of the arteries was determined by palpation of accessible arteries, by ophthalmoscopic examination, and by roentgenologic evidence of calcification of the aorta. From Table V it appears that arteriosclerosis has no consistent influence on the outcome of cucurbocitrin therapy when present but that just as in the case of cardiac damage its absence makes for a favorable prognosis. In both groups only one patient without thickening of the arteries failed to respond to treatment.

*Significance of the Menopause in Females in Relation to Success of Cucurbocitrin Therapy.* Fortunately, over two-thirds of the patients in this series are females and the success and failure of treatment in these were analyzed from the standpoint of onset of hypertension before or after the menopause and also in relation to the menstrual status at the time of treatment. By a casual examination of Table VI one gains the impression that patients with hypertension and regular catamenia respond somewhat better to cucurbocitrin therapy both so far as lowering of the blood pressure and symptomatic relief are concerned. And also that high blood pressure yields more readily in patients in whom the onset of hypertension preceded that of the menopause. However, by a more careful analysis of other possible factors which are known to influence the response of patients to this treatment we find that age and duration of hypertension prior to treatment can readily account for all noted differences. For instance, the average age of patients in the group where hypertension preceded the menopause is 43.7 years while the age of the group in which menopause came on before hypertension is 56.8 years. Similarly the average duration of hypertension in the group with regular catamenia is 2.9 years, while in the group with menopausal symptoms it is 5.7 years, and in the group past their menopause it is five years.

*Dosage of Cucurbocitrin and Success of Treatment.* As previously mentioned, the standard dose of cucurbocitrin was 50 mg. three times a day. In view of the fact that the immediate fall in blood pressure following a single dose of the drug was in proportion to the size of the dose, larger doses were tried in several patients after their systolic blood pressure had been decreased with ordinary doses by 10 to 41 mm. for some time. Among 7 patients who received 100 mg. three times a day the blood pressure remained unchanged in 5 and in 2 instances it came down further by 10 and 26 mm. respectively without appreciable further symptomatic improvement. In 1 of the 5



TABLE V.—RESULTS OF CUCURBOCITRIN TREATMENT OF HYPERTENSION IN THE LIGHT OF CARDIOVASCULAR DAMAGE.

Group of patients.	Degree of cardiac involvement.						Arteriosclerosis.					
	Marked.		Moderate.		None.		Marked.		Moderate.		None.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Blood pressure reduced 10 mm. or more . . . . .	8	28	16	55	5	17	13	45	11	38	5	17
Blood pressure unchanged . . . . .	4	36	6	55	1	9	3	27	7	64	1	9
Symptomatic relief obtained . . . . .	10	31	17	53	5	16	12	38	16	50	4	12
No symptomatic relief . . . . .	2	29	5	71	..	..	4	57	2	29	1	14

TABLE VI.—SIGNIFICANCE OF THE MENOPAUSE IN FEMALES IN RELATION TO RESULTS WITH CUCURBOCITRIN IN HYPERTENSION.

Group of patients.	Menstrual status.						Onset of hypertension in relation to the menopause.					
	Catamenia regular.		Menopausal symptoms.		Menopause past.		Hypertension before menopause.		Menopause before or with hypertension.			
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Blood pressure reduced 10 mm. or more . . . . .	6	75	4	67	9	69	10	77	9	64		
Blood pressure unchanged . . . . .	2	25	2	33	4	31	3	23	5	36		
Symptomatic relief obtained . . . . .	7	100	4	67	11	85	10	83	12	85		
No symptomatic relief . . . . .	..	..	2	33	2	15	2	17	2	15		

patients the dose was later increased to 150 mg. three times a day without any change in blood pressure or subjective feeling. It is of interest to note here that this was the same patient whose systolic pressure showed an immediate fall of 16 mm. after 50 mg. of cucurbocitrin and one of 26 mm. after 100 mg. of it. The explanation of the failure of larger doses of cucurbocitrin in most instances to decrease blood pressure below a certain level achieved by smaller doses of the drug probably lies in a certain individual minimum of pressure necessary for proper function. Below this level nothing short of shock will reduce the blood pressure for any length of time. Herein seems to lie one of the chief limitations and at the same time a most important safeguard of symptomatic treatment of hypertension.<sup>4</sup>

*Untoward Effects of Cucurbocitrin Therapy and the Question of Tolerance.* No undesirable effects of cucurbocitrin administration from excessive lowering of the blood pressure or toxic action of the drug were observed in any of the treated patients. In successful cases the same dose of cucurbocitrin was as effective after continuous administration over a period of several months as at the beginning of treatment.

*Duration of the Effects of Prolonged Cucurbocitrin Administration.* In twenty successful cases cucurbocitrin therapy was discontinued and the patients observed at weekly intervals for rise of blood pressure and return of symptoms. In 12 cases the effects of treatment were known to persist from a week's to a month's time. In 7 cases the benefits of treatment lasted from one to three months, and one patient retained a normal blood pressure and was symptomless for five months.

It is noteworthy that hypertension returned before the appearance of subjective symptoms in 10 cases, whereas the reverse was observed only in 2 patients. An investigation of clinical data having a possible bearing on the duration of the beneficial action of cucurbocitrin brought out the fact that all cases in which hypertension was held in check for one month or more after discontinuation of medication were in women. On the other hand, the group in which the blood pressure began to rise during the first month\* included about an equal number of males and females. Parallel with this goes the observation that in 63 per cent of women who responded for longer periods of time the onset of the menopause preceded that of hypertension. On the contrary, in those who benefited only for periods up to one month hypertension preceded the menopause in 83 per cent and in the remaining 17 per cent the discovery of high blood pressure by instrumental means coincided with the first menopausal symptoms, but probably in reality was present earlier. These findings, if confirmed by further observations, would

\* Here are also included cases without relapses which could not be followed longer than one month.

mean that more lasting benefits can be obtained by cucurbititrin in cases of hypertension, the onset of which occurred after the menopause.

Other differences noted between these two groups of patients were that 'phthalein excretion was somewhat higher and cases free from arteriosclerosis were four times as numerous in the group which derived more lasting results from treatment with cucurbititrin. How great a part in the response of this group can be ascribed to these features, *versus* the onset of hypertension in relation to the menopause, is difficult to say.

*Value of Cucurbititrin Therapy.* Cucurbititrin is a valuable drug in the symptomatic treatment of hypertension because it produces lowering of high blood pressure and gives subjective relief in a large proportion of cases. The desirability of removing, or at least diminishing, the extra load carried by the heart in hypertension is obvious. In addition, secondary vascular-renal degenerative changes may be prevented or their progress slowed down. Symptomatic improvement of many patients under cucurbititrin therapy was so marked that usefulness and enjoyment of life were restored to those who were practical invalids.

The simplicity of administration and absence of any undesirable effects are additional advantages of this drug.

*Results of Cucurbititrin Therapy Compared to Those of Liver-extract Injections.* A complete report of results obtained with liver extract in the treatment of hypertension having appeared elsewhere,<sup>4</sup> we shall limit ourselves here to a brief comparison of the results obtained with these two preparations. From Table VII, in which all cases in both series are compared, it appears that reduction of high blood pressure follows cucurbititrin therapy in a slightly higher percentage of cases, but that the average lowering of the blood pressure is somewhat greater after liver-extract medication. Symptomatic relief is also obtained slightly more often with cucurbititrin, while "complete" and "marked" relief of symptoms follows with equal frequency the administration of both drugs. As regards the duration of improvement after either therapy is discontinued, the beneficial results of liver-extract injection appear to last somewhat longer than those of cucurbititrin medication.

Turning to an appraisal of the two substances in the 21 cases in which they were used consecutively, we see that cucurbititrin held the ground gained by liver-extract therapy in all but 2 cases and liver-extract administration after cucurbititrin accomplished the same in all cases except one. In addition out of 14 cases which were treated with liver extract first cucurbititrin produced an additional lowering of the blood pressure between 15 and 23 mm. in 7 cases. Symptomatic relief over that produced by liver extract was observed from cucurbititrin in 4 cases. On the other hand, liver extract when given to 7 patients who previously received cucurbititrin brought

about additional lowering of the systolic pressure of 17 mm. in one case only. Greater symptomatic relief while on liver extract was reported by two and less by one patient in this group of 7 cases.

No direct comparison between the action of the two drugs in these groups can be made, because the group which received liver extract first comprises a greater proportion of failure cases with this method (64 per cent as against 43 per cent of initial failures with cucurbititrin). However, the success of one preparation after the failure of the other was seen with sufficient frequency to justify a trial with both in refractory cases.

A comparison of individual clinical features making for success or failure of treatment with cucurbititrin and liver-extract brings to our attention a striking similarity between these two series. With the exception of age, which is unimportant in liver-extract therapy, and duration of hypertension, which in liver-extract cases is significant also in regard to lowering of hypertension, the agreement of all statistical data in the success and failure groups is practically complete.

The above comparisons lead us to the conclusion that outside of minor differences the clinical results of cucurbititrin and liver-extract therapy are essentially similar, both in kind and degree. The explanation of this must be looked for first in the same pharmacologic action of these drugs which consist of a sustained dilatation of the smallest units of the peripheral vascular system. And, second in their symptomatic rather than etiologic mode of attack on hypertension, which precludes the lowering of high blood pressure below the safe level necessary for adequate function. Both preparations accomplish more in the symptomatic treatment of hypertension than any other methods in the experience of the authors, but the effects of both can extend only so far and no farther, as long as the underlying cause of hypertension is not removed.

**Summary.** 1. A brief pharmacologic review of cucurbititrin is given.

2. Examination of patients and the method of administration of cucurbititrin are outlined.

3. (a) The immediate effect of a single oral dose of cucurbititrin in hypertension cases is a fall in the systolic and diastolic blood pressure. The extent and duration of this fall are roughly in proportion to the dose in the same patient.

(b) After prolonged administration of cucurbititrin in 40 cases of hypertension it was found that a reduction of the average systolic pressure by 10 mm. or more took place in 73 per cent of cases, and that the average reduction of the systolic pressure in these cases was 29 mm., and that of the diastolic pressure 15 mm.

(c) Out of 39 cases with symptoms referable to hypertension definite relief was obtained in 82 per cent of cases.

TABLE VII.—RESULTS OF CUCURBOCITRIN THERAPY COMPARED TO THOSE OF LIVER-EXTRACT INJECTIONS.

Treatment.	Blood pressure reduced 10 mm. or more, per cent.	Average reduction of blood pressure.		Symptomatic relief.		Duration of effects.			
		Systolic, mm.	Diastolic, mm.	All degrees, per cent.	Complete and marked, per cent.	Under 1 month.		Over 1 month.	
						Cases.	Per cent.	Cases.	Per cent.
Cucurbitrin, 40 cases	73	29*	15	82	55	12	60	8	40
Liver extract, 27 cases	63	33	19	76	56	3	37	5	63

\* Corrected, see text.

4. The average age of patients who responded to cucurbocitrin therapy was lower than that of the failure group. Sex, the degree of hypertension, and body weight were unimportant. On the other hand, the duration of hypertension prior to treatment was found to be twice as long in the group of patients who obtained no symptomatic relief than in the group that did.

Data in reference to the degree of kidney involvement were not sufficiently decisive to warrant any conclusion.

Cardiovascular damage when present had no consistent influence on the outcome of treatment, but its absence almost always made for a favorable prognosis.

There was no apparent connection between the menopause in female patients and the success of cucurbocitrin therapy save that in all cases in which improvement after discontinuation of the drug lasted for over a month the onset of the menopause preceded that of hypertension.

5. No untoward effects after cucurbocitrin or signs of tolerance to the drug were observed.

6. The effects of prolonged cucurbocitrin administration lasted after the drug was stopped from one week to one month in 11 cases, and from one month to five months in 8 cases.

7. Cucurbocitrin produced lowering of the blood pressure and symptomatic relief in a somewhat larger per cent of hypertension cases than did liver extract's but liver extract reduced the blood pressure to a slightly more marked degree. There also was a striking similarity between the clinical features making for success or failure of treatment with both preparations.

**Conclusions.** 1. Cucurbocitrin therapy in hypertension causes considerable lowering of the blood pressure, and gives complete or marked relief of symptoms in a majority of cases.

2. Patients under the age of fifty years, with known duration of hypertension of less than three years, and having little cardiovascular damage are most likely to respond favorably to cucurbocitrin.

3. The effects of cucurbocitrin and liver extract in hypertension are essentially alike in kind as well as degree and apparently both are based on sustained peripheral vasodilatation.

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## ACUTE LEUKEMIA: A REVIEW OF THE LITERATURE AND OF TWENTY-EIGHT NEW CASES.

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A SEARCH of the literature since 1917, when Gorham reviewed 28 autopsied cases of acute myelogenous leukemia, indicates that acute leukemia can no longer be considered a rare disease. The reported cases now number nearly 500. Only 85 cases could be found in this large group which had been proved by autopsy, but there were some cases reported in foreign periodicals which could not be consulted, and it is probable that these would bring the total number of autopsied cases of acute leukemia well up to the hundred mark. I can add to this number 28 new autopsied cases which were treated within the last ten years at the allied hospitals of the Harvard Medical School and at the Strong Memorial Hospital of Rochester, New York. One particularly illuminating case will be cited in detail; while study of the others has influenced the statements made in this paper. Their data have not been included for the sake of brevity.

In this study, acute leukemia is considered as a definite clinical syndrome as distinguished from the two types of chronic leukemia. There is indicated in the discussion the probability that most cases of acute leukemia are of myelogenous origin, but it must be emphasized that a distinction between a lymphogenous and myelogenous origin is often impossible in this acute syndrome. The 28 new cases and those reported in the literature, since 1917, show a wide divergence in diagnoses. Twenty-four per cent were diagnosed as acute myelogenous leukemia, 32 per cent as lymphogenous, 34 per cent as acute leukemia, and 10 per cent as special forms, yet they all followed the usual text-book picture of the acute leukemia syndrome: onset with weakness, a "coryza" or some obscure infection, fever, prostration, bleeding, purpura, adenopathy, splenomegaly, leukocytosis, anemia, immature leukocytes in the blood, leukemic masses and fatal termination.

It is apparent from this that there is no essential difference in the clinical picture of acute leukemia, whether the case has been diagnosed as acute myelogenous or lymphogenous leukemia. The wide divergence in diagnosis in all of these cases of acute leukemia is due to the difficulty in differentiating the immature cell forms so that it is practically impossible to separate the cases into the usual two

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types. Older immature cells of myelogenous origin, that is, myelocytes, can be recognized by their granules with both polychrome stains and oxydase preparations. Nongranular mononuclears, however, whether lymphoblasts or myeloblasts, do not show oxydase granules and are frequently taken for large atypical or abnormal lymphocytes, though Sabin<sup>15</sup> has shown that at least one type of these nongranular mononuclears is a myeloblast.

Changes in the appearance and number of the white blood cells during the course of the disease may cause further confusion in diagnosis. In many of the cases, at the onset of the disease, the blood smears have shown large numbers of granular myelocytes and a few large atypical nongranular mononuclears. Later this situation has been reversed until, finally, the myelocytes have almost disappeared and the large nongranular forms have predominated. This phenomenon has been described by Reh<sup>14</sup> as acute "myelogenous lymphoid" leukemia, and by Logeheil<sup>10</sup> as mixed leukemia. Ewald, and others,<sup>3</sup> under the title "acute monocyte and stem-cell leukemia," and Lasch<sup>9</sup> ("acute myeloblastic leukemia") attempt to go further upon the basis of morphology alone in recognizing immature cell types. But a comparison of the pictures or plates in the articles of the various authors will convince any critical observer that the differentiation between the immature nongranular cells upon a purely morphological basis is unsafe and perhaps unsound. Myeloblasts cannot readily be distinguished from immature lymphoid cells except by some differential staining method like that used by Sabin;<sup>15</sup> acute cases of about two weeks' duration may have from 60 to 100 per cent of nongranular cells of all sizes and shapes in the blood, varying in number from 1000 to 1,000,000 per c.mm. Sabin<sup>16</sup> points out that there is a variation in size of the myeloblasts "from a cell whose diameter is more than twice that of a red blood cell to one even smaller." Distortion, by smearing and drying of fresh blood or smears from organs, tend further to complicate the picture, and, to the inexperienced observer, the identification of cells becomes extremely difficult. Leukopenia may develop or exist throughout the period of observation of cases of acute leukemia which often leads to diagnostic errors.

The origin of myelocytes and the differentiation of the younger types of these cells are still in controversy and beyond the scope of this report. The stages of this controversy can be traced in the predominance of a certain diagnosis over a definite period of time. Up to 1910, acute myelogenous leukemia was more frequently diagnosed than lymphogenous, and the nongranular cells were called myeloblasts. Then there was a period of doubt for the next ten years, when for the most part, strictly similar cases were called lymphogenous, the nongranular cells being called lymphoblasts, and the myeloblasts either ignored or forgotten. Now the clinician and the pathologist are more cautious and are apt to make the diagnosis



simply that of acute leukemia with qualifications. Probably within the next five years, myelogenous leukemia will be thought more frequent than the lymphogenous type.

Autopsy findings in the gross help little to determine the origin of the disease as there is obvious splenic, lymph-node, and bone-marrow involvement in varying degree in all cases. On microscopic examination of the tissues, it is usual to find all of the organs infiltrated with leukemic cells, frequently in numbers large enough to cause atrophy of the normal structures. One is often at a loss to differentiate these cell types because the morphology is no more distinctive in the tissues than in the blood stream; thus the pathologists usually avoid the issue and state that the cells resemble lymphocytes or myeloblasts, and the like.

Ewing<sup>1</sup> emphasizes that "the lesions of leukemia, both lymphocytic and myelocytic, involve the bone marrow, lymph nodes, spleen and other preëxisting lymphoid tissues. The picture is that of a diffuse *systemic* involvement of blood-forming organs with secondary invasion of other tissues."

Different pathologists classify the same leukemic-cell infiltrations or "leukemic" masses under such different terms as leukoblastoma, myeloblastoma, leukosarcomata, lymphomata, lymphoblastomata, malignant lymphomata, and so forth, each term reflecting a slightly different idea of the origin of the cells involved. Others have classified, in special groups, those cases with lesions or masses in certain specific regions although the location of the lesions does not necessarily indicate a difference in etiology; that is, "Sternberg's leucosarcomatosis" for a leukemia with a mediastinal leukemic mass.

In the survey of the reported and the new cases, the general impression was obtained that the leukemic process brought about a generalized infiltration of the organs by the leukemic cells, and the lesions were rather stereotyped. Certain unusual manifestations, however, are of particular interest. Osler, in 1892, recorded nodular masses of leukemic cells in the base of the tongue, the stomach mucosa, and the lung parenchyma; otherwise these do not seem to have been noted in the literature. Nodules in the skin have been reported by Ward,<sup>17</sup> Joachim,(1917) and others though they are relatively uncommon. Four of the 28 new cases reviewed here had leukemic nodules in the skin as a prominent feature. There were 2 cases with nodules in the lungs. 4 cases with extensive central nervous system infiltration accompanied by fatal cerebral hemorrhage, 3 cases with large nodules in the heart, and 2 cases with large mediastinal masses (Sternberg's type). One case, a boy, aged nine years, was found to have nodules in all of his organs, and in addition such an extensive and massive infiltration by the leukemic cells as to make up quite an appreciable part of his total body weight. From one-third to one-half of every section taken was composed of these atypical, immature, nongranular cells. Retroperitoneal masses were also not uncommon.

For the purposes of analysis of these cases, the onset of the disease is arbitrarily taken from the first symptom obviously due to the leukemia. The leukemic process probably had been present for some time before this was manifested. The duration of the disease is indicated in Chart I. The sharp grouping of 84 per cent of the

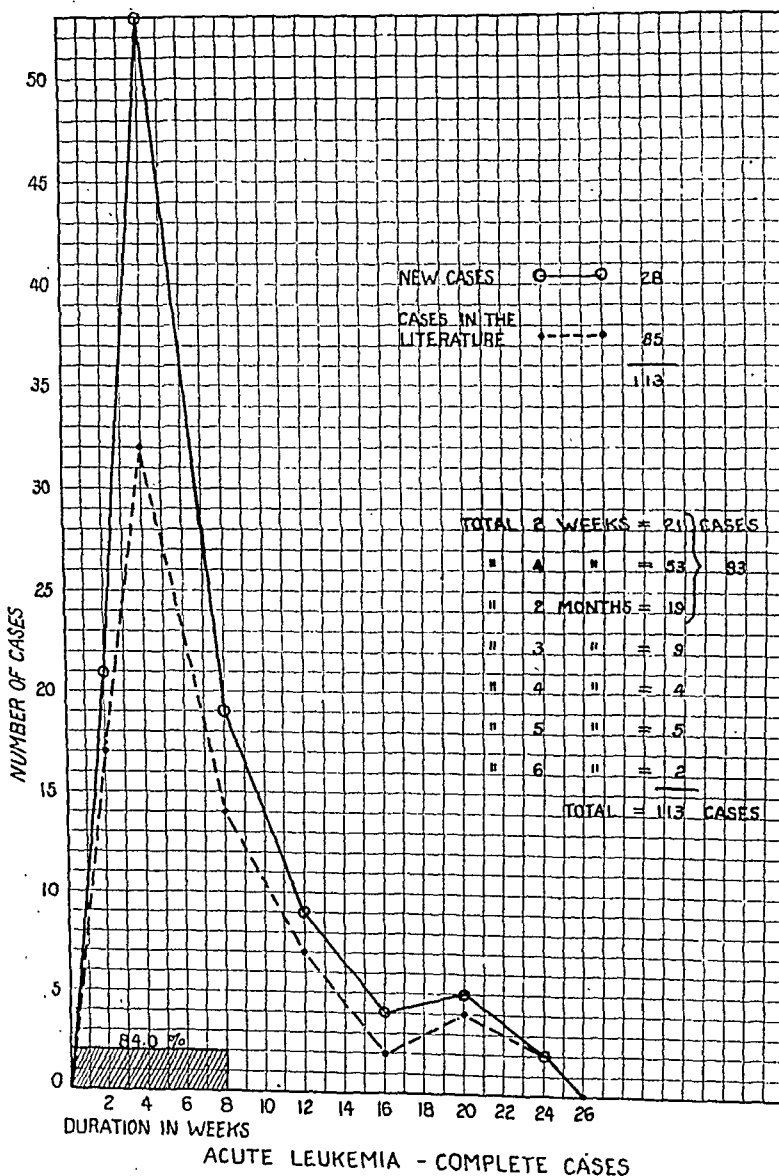


CHART I.—Showing the duration of the illness of 113 autopsied cases of acute leukemia.

cases within the first eight week period is very striking. Of the total of 113 cases of acute leukemia (85 reported in the literature since 1917 and 28 new cases reported here) 21 (18.5 per cent) died within two weeks after the onset of the acute symptoms, showing the devastating effect of the process once it is under way. These

figures agree with those reported by Minot and Isaacs<sup>12</sup> and Ward<sup>17</sup> who analyzed the cases upon the basis of the clinical diagnosis only.

A study of the age incidence of the 113 cases (Chart II) reveals that the disease is particularly apt to occur at three different periods in life; namely, up to ten years of age (24 per cent), between 25 and 35 (42 per cent), and between forty-five and fifty years of age (20 per cent).

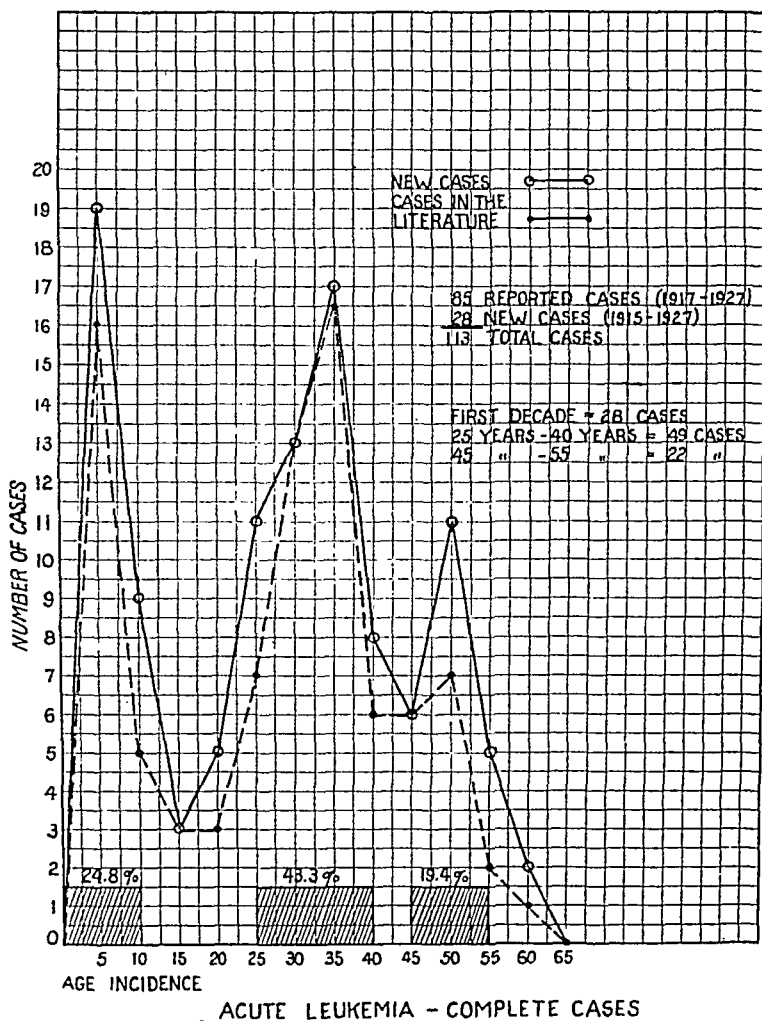


CHART II.—Showing the age grouping of the autopsied cases of acute leukemia.

Acute leukemia seems to be a disease of *males*. They predominate in a ratio of almost 2 to 1, throughout. Among the cases lasting for less than two months (Chart I) 61 per cent occurred in males and of those patients who had the disease for three to six months, 76 per cent were males. Of the patients under ten years of age, 69 per cent were males and 61 per cent of the patients between twenty-five and thirty-five years of age were males. On the contrary between

the ages of forty-five and fifty years, there are 8 females and 3 males, a ratio of about 3 to 1, which indicates a predilection of the disease for females at the *menopause period*, as in both of the other groups, two-thirds of the cases occurred in males.

In summarizing information concerning the prodromal period, many apparently unrelated symptoms may be the first symptoms of acute leukemia. There are, however, three very common complaints which stand out as predominant early symptoms of this disease. The patient frequently consults a throat specialist because of sore throat and enlarging tonsils. If the leukemia is unrecognized, the tonsils may be removed. This is frequently followed by severe, prolonged hemorrhage because of the marked decrease of the blood platelets. Thirty to 40 per cent of the patients have had a prolonged hemorrhage after tonsillectomy, dental extraction, or some trifling operation leading to exsanguination.

Ulcerative stomatitis is frequent in the early stages of acute leukemia, the ulcerative lesions involving the pillars of the tonsils, the tongue, and the posterior pharynx. The organisms of Vincent's angina (bacilli and spirilli) occurred in about 50 per cent of the cases under review. In nonleukemic cases, such a stomatitis may be accompanied by a blood picture roughly resembling that of acute leukemia.

In somewhat over 50 per cent of the cases of acute leukemia, shortly before the onset of the first symptoms attributable to leukemia, there was a history of respiratory infection, sometimes classified as a "cold," "the grippe," "bronchitis," or the like. This infection is recorded usually as "hanging on" and "failing to respond to treatment." There is usually more prostration than there is reason to expect, and the severity of the symptoms remains unexplained until the leukemia is recognized.

The following case is briefly summarized as the most unusual of the group because of the nodules in the skin, stomach mucosa, lung parenchyma, and retroperitoneal regions, and the absence of any extensive hemorrhage. The blood was studied in great detail.

**Case Report.** A woman, aged fifty-six years, for three months, had had a series of "colds" and a feeling of weakness. The past history has no bearing upon the present illness. Two weeks previous to entry, hoarseness and aphonia developed. One week later, a crop of "small lumps" suddenly appeared in the skin over the chest and abdomen "almost in a day." The spleen was not palpable, and a white blood-cell count then was 70,000 per c.mm. The patient rapidly became weak and stuporous and was sent into the hospital.

On admission the patient was semicomatose; temperature 100.4° F. The skin was darkly pigmented and did not show pallor. There were several petechiæ over the shoulders and the buttocks. Many discrete nodules were found in the skin over the chest, abdomen, and back. They varied from 1 to 6 mm. in diameter, were slightly elevated, were lilac or pinkish in color, and seemed confined to the skin or superficial tissue. The tonsils were large and red but not ulcerated. The submaxillary lymph nodes were

the only lymph nodes palpable. The spleen was felt 4 cm. below the left costal margin, firm, not tender. The liver was palpable 4 cm. below the right costal margin. The rest of the examination was essentially negative.

Blood findings were as follows: Hemoglobin 65 per cent (S); red blood cells 2,900,000 per c.mm.; white blood cells 180,000 per c.mm., of which 90 per cent were atypical, nongranular mononuclears. The blood platelets were markedly diminished.

The urine was positive for Bence-Jones protein.

The next day, the patient was irrational, oozing of blood occurred from the gums, new ecchymoses appeared, and there was an increase in the size of the lumps in the skin. The skin was waxy in appearance. A generalized adenopathy of small discrete nodes was noted. The spleen increased in size and was palpable for 8 cm. below the ribs, almost level with the iliac crest. It seemed to have doubled in size within twenty-four hours. The liver remained unchanged. The white blood cells were 141,700 per c.mm.

The spleen was irradiated in an attempt to aid the patient temporarily. Eight hours after the radiation all bleeding from the gums had stopped and the spleen had decreased to about half of the previous size. The patient became stuporous, and exitus occurred twelve hours after the radiation had been given, without further changes being noted, though the patient was frequently examined.

**Laboratory Data.** Blood withdrawn by vein puncture was grayish-brown and viscous and, added to powdered potassium citrate, became stringy and rubbery before it could be centrifuged; no definite firm clotting occurred at any time. No clot retraction occurred even after one month's time. The bleeding time averaged from five to fifteen minutes. In a blood smear, when the white blood count was 141,700 per c.mm., the white blood cells seemed almost equal in volume to the red blood corpuscles. Three differential counts of white cells stained with Wright's stain on each of three days averaged: Neutrophilic polymorphonuclears, 2 to 7 per cent; young neutrophilic polymorphonuclears, 2 to 7 per cent; small normal lymphocytes 3.5 to 6 per cent; neutrophilic myelocytes 8 to 12 per cent; eosinophilic myelocytes 8 to 12 per cent; large (nongranular) myeloblasts (Figs. 1 and 2, identified by Sabin's vital staining technique) 54 to 66 per cent; medium sized nongranular mononuclears, larger than small lymphocytes, 13 to 20 per cent. Peroxydase blood smears (Goodpasture's stain) showed 8 to 12 per cent of fairly large cells with large numbers of small granules packed around an indistinct oval or kidney-shaped nucleus and 4 to 7 per cent of similarly shaped cells with one to six rather large granules. There were many cells of similar appearance without any oxydase granules. The total percentage of mature cells and myelocytes demonstrated with the Wright's and supravital stains varied from 14 to 25 per cent, so that the discrepancy between these two methods is not marked insofar as the identification of fairly mature cells is concerned.

The red blood cells showed marked anisocytosis and poikilocytosis, a moderate amount of achromia, and occasional polychromatophilia. Microcytes were rare. Nucleated forms were seen occasionally. Blood platelets were few, small, and poorly stained.

**Clinical Diagnosis.** Acute leukemia, probably myelogenous. Probable duration three months, although definite symptoms occurred for only about four weeks.

**Autopsy.** (Dr. William McNamara.) The body was that of a well-developed and nourished middle-aged white female. The skin of the entire body was studded with small, purplish tumor masses, the largest being about one-half centimeter in diameter. All the superficial lymph nodes were palpable, several in the neck being enlarged to 3 cm. in diameter. Two distinct tumor masses were felt in the abdomen. The tonsils were enlarged and of a dark-purple color. Numerous purplish masses were seen



FIG. 1.—(Oil Immersion) (Untouched microphotograph of blood smear stained with Wright's stain.) One neutrophilic myelocyte is at the top with a medium sized, nongranular mononuclear beneath it. At right, near bottom, is a large nongranular mononuclear identified by supravital stains as a myeloblast, Sabin's type A. Three other medium sized mononuclears are below and to the left of this.

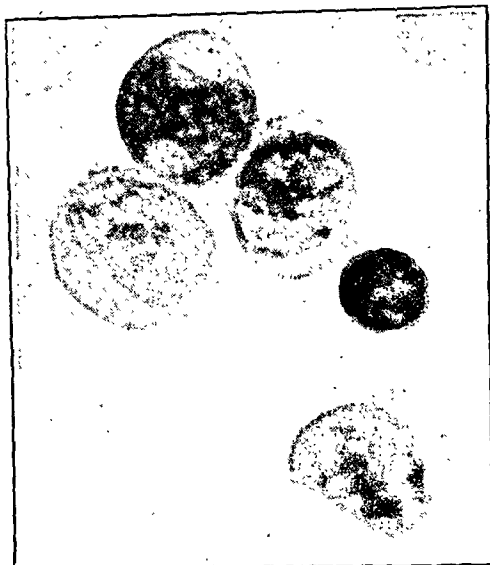


FIG. 2.—(Oil Immersion). Untouched microphotograph of blood smear stained with Wright's stain. The small dark cell resembles a small lymphocyte. The remaining four cells are large, nongranular, mononuclears identified as myeloblasts by supravital stains.



FIG. 3.—The dark, purplish, leukemic masses in the tonsillar ring.

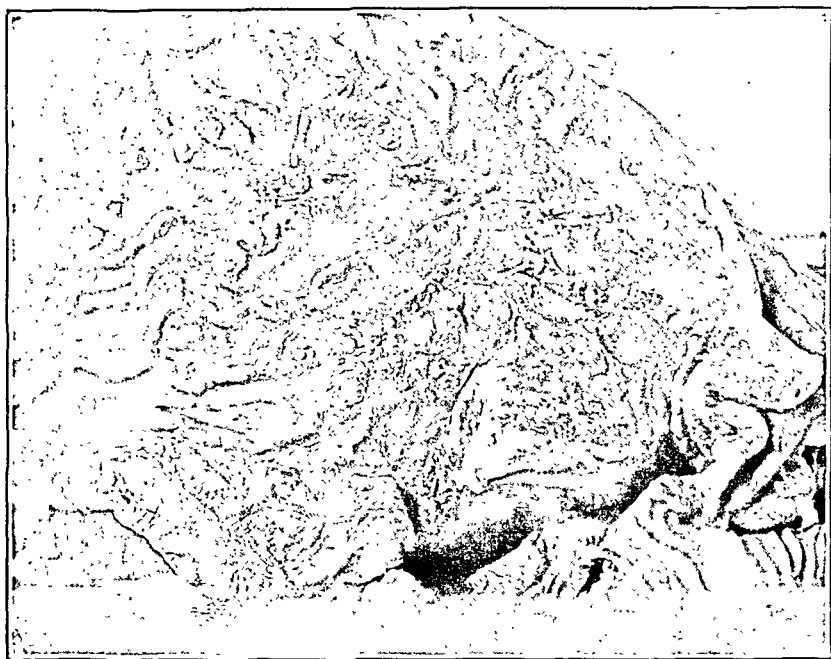


FIG. 4.—There are six large, dark, purplish masses from 1 to 1.5 cm. in diameter and many (50 or more) from 2 to 4 mm. in diameter spread over the stomach mucosa. These are composed of leukemic cells.

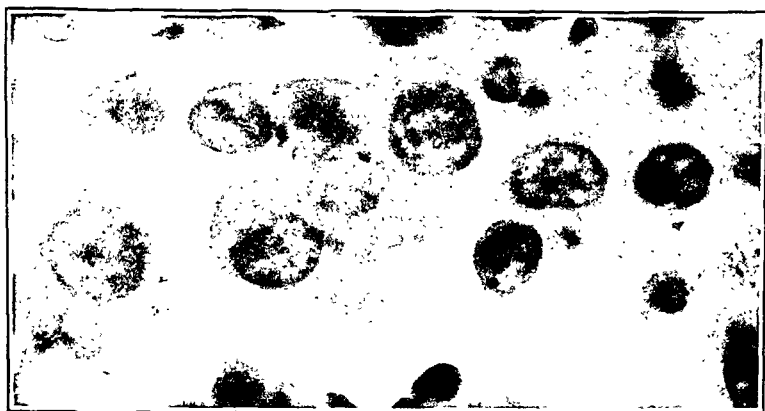


FIG. 5.—(Oil Immersion). Section from a small tumor mass in the liver (Hematoxylin-eosin stain.) In the middle of the picture from the left edge to the right is a series of cells apparently young myelocytes and myeloblasts. The nuclei are large, round, or oval and the cytoplasm is voluminous and slightly basophilic and without granules. The smaller cells suggest lymphocytes. The larger resemble the myeloblasts and myelocytes found in the peripheral blood.

on the posterior portion of the tongue in the tonsillar ring (Fig. 3). When the abdomen was opened, two tumor masses were seen, one in the retro-peritoneal tissues, measuring about 8 by 4 by 4 cm.; the other situated in the omentum, measuring 3 by 4 by 4 cm. Both were of a cherry-red color. On cut-section these tumors presented a soft, purplish, homogeneous, pulpy surface from which very little blood exuded. All the abdominal lymph nodes were enlarged and purplish-gray in color on section. The spleen extended down to the costal margin. The pleural cavities contained no excess of fluid. Nothing was noted superficially except the dark-purplish color of the lungs and the numerous purple areas studded throughout the pleura.

The lungs were heavier than normal. Both were air-containing and, on cross-section, showed numerous small purplish pectechiæ and purplish nodular areas about 2 to 5 mm. in diameter which were thought to be due to leukemic-cell masses.

In the kidneys and the liver, no gross lesion could be seen, though a grayish-white infiltration seemed present throughout these organs with some distortion of the normal architecture.

The spleen weighed 400 gm. and was quite firm and bluish in color. There were no adhesions to its surface. On cross-section, the pulp was soft and purplish and scraped off readily. The Malpighian corpuscles and the normal structure were poorly defined due to an increase in pulp substance.

The stomach mucosa was studded with dark, purplish-blue, tumor masses about fifty in number, the average being about 3 mm. in diameter. There were several larger masses of about 1.3 cm. in diameter in the antrum. These tumors were were all umbilicated and the larger showed some superficial ulceration (Fig. 4). On cross-section, they were firm, homogeneous, and dark purple in color. Very little blood exuded from them. There were a few similar nodules in the lower intestinal tract, not related definitely to the lymphoid structures.

The bone marrow of the center of the femur and the ribs was dark red, gelatinous, and extremely cellular. The ribs were thin and cut easily as if osteoporosis had occurred.

The remainder of the organs showed no gross abnormality related to the leukemia.

The most interesting aspect of this case was found in the microscopic study of the leukemic cells and their distribution. There was a general infiltration of every organ examined, by leukemic cells which resembled the small lymphocyte in size and shape but possessed a more abundant cytoplasm which stained pink with hematoxylin-eosin. Some of these cells had a nucleus very similar to that of a myelocyte (Fig. 5), but no granules were seen in the pinkish cytoplasm. There were no granules in similar cells which were thought to be myeloblasts. Oxydase granules did, however, occur in many of the cells from smears of the various organs. The following percentages of cells contained oxydase granules, and they probably were myelocytes: Bone marrow, 80 per cent; spleen, 40 per cent; liver, 10 per cent.

The peculiar purplish or grayish appearance found in the lungs, liver, kidney, stomach and other organs was caused by neoplastic-like infiltration by this large nongranular mononuclear cell (Fig. 5) which apparently is a myeloblast or primitive cells of bone-marrow origin. The various cells found in the organs are shown in Fig. 5, and their appearance suggests a transition of some form of primitive cells to early forms of myelocytes. The bone marrow of the center of the femur and the normally inactive parts of the ribs which were extremely cellular contained only cells in a more or less embryonic state. The predominating cells seemed identical to the primitive cells in the blood cells thought to be myeloblasts, though a few myelocytes were found in most of the sections.



There was another type of cell found only in the two large, cherry-red abdominal tumors. This cell was similar in all of its characteristics to an erythroblast. It was much larger than the predominating cell of the other tumors. The cytoplasm stained a faint red with hematoxylin-eosin but was nongranular, and the nucleus was small and dark. In some instances, the nucleus was seen to be partly extruded. The cells contained iron as demonstrated by special stains, so that apparently these cells were some early form of an erythrocyte containing hemoglobin.

**Autopsy Diagnosis.** Acute leukemia—probably myelogenous (primitive-cell type) with masses of leukemic cells infiltrating all of the body tissues.

**Discussion.** With the oxydase stain, then, the myelogenous cell types have been traced back to a nongranular cell resembling a large lymphocyte but with more cytoplasm than large lymphocytes have and with either a round or an indented nucleus. There was also an undifferentiated cell type smaller than this with a relatively large amount of cytoplasm and no oxydase granules.

Two explanations offer themselves. Either this later cell is the originator of all myelogenous cells, which, by virtue of the overwhelming demand for cells, is thrown out into the circulation in its primordial state; or, due to the same urge, lymphoblasts are stimulated to multiplication and are thrown out before maturation. Against the latter, though not proof, is the lack of balance in numbers between lymphogenous and myelogenous cells in the smears. No cells could be positively identified as normal, mature, large lymphocytes. Except for the cells containing oxydase granules, the blood cells, in this case, are difficult to tell from those of the acute lymphatic leukemia, except by the supravital staining technique, and even then certain doubt arises concerning the status of exceedingly primitive stem cells.

Dr. C. A. Doan very kindly studied several live-blood preparations from this case, using the supravital staining technique, and demonstrated the neutral red granules in the large, immature cells which were nongranular with Wright's stain and which showed no per-oxydase granules. It was his opinion that these cells were myeloblasts and similar to those described by Sabin and Doan and others<sup>16</sup> in a case of chronic myelogenous leukemia in an acute phase.

Since the autopsy disclosed cells of an undifferentiated type packed in every available space in all of the body tissues and since cells resembling erythroblasts were likewise noted, this would seem to indicate that it was a primitive or "stem" cell with the ability to differentiate into several types, and seems to offer some support to the theory of the single-cell type as an origin for all blood cells. It also suggests a neoplastic process because very malignant tumors commonly revert to very simple undifferentiated cell types or in extreme instances to differentiate toward one- or several-cell types. The pathologist, in trying to differentiate these cases by the morphology of the cells, is almost as much at sea as the clinician, especially in differentiating the immature-cell types.

The cases under review here showed evidence of a wide disagree-

ment as to the classification of similar cell types. The cells in the blood and tissues usually have been classified strictly from their morphologic appearance, and the opinion and diagnosis of the clinician has seemed in many cases to have influenced the pathologist in his classification. The late Dr. J. Homer Wright (personal communication) has called these abnormal immature cells "bastard cells" in that they defy classification at present. It is possible that, in the acute leukemias, the cells predominating are thrown out before they have been able to mature and differentiate. If the "single-cell" theory is correct, there may be no possibility of separating some of the cases of acute leukemia into such types as are clearly defined in the chronic cases.

Until hematologists and pathologists come to an agreement upon blood-cell types and their origin, and this presupposes that we have a simple, differential method of recognizing these types, the differential diagnosis between different types of acute leukemia will be difficult to make. The supravital staining technique,<sup>16</sup> if it is more generally used, would demonstrate that usually in acute leukemia the mononuclear cells are myeloblasts occasionally monocytes and seldom lymphocytes. Apparently most of the acute cases on record that have been diagnosed as lymphogenous could just as well be called myelogenous leukemia or *vice versa*, because there is no definite difference between them in the onset, progress, signs and symptoms, blood findings (without the supravital technique), and autopsy descriptions. There are differences in degree only. In both types of leukemia, the abnormal cells infiltrate all the organs to a varying degree. The diagnosis depends entirely upon the cell type in the circulating blood and in the tissues. Cell masses (lymphomata) may occupy the lymph nodes, the region of the thymus, the retroperitoneal structures, and the various organs, much in the manner of a neoplasm. The duration is so short and the stimulus to produce cells so great that the appearance of the cell masses is decidedly neoplastic. The process concerns an atypical, primitive, or embryonic cell-type which is acting much like a neoplasm so that all of the various primitive and atypical forms are to be seen in the tumors or cell masses.

As a general rule for the present, it may be wiser, in the clinic, to disregard the precise classification of these very immature cells in the cases of acute leukemia until their status is more definitely settled and to avoid confusion and fruitless discussion by recognizing only the primitive nature of the predominant cells.

**Conclusions.** From 113 autopsied cases of acute leukemia, (85 reported in the literature since 1917 and 28 new cases reviewed here) the following conclusions can be drawn:

1. Acute leukemia is not a rare disease.
2. The constancy of the history, course, clinical, blood and tissue findings in acute leukemia is noteworthy, regardless of whether the case is considered to be of myelogenous or lymphogenous origin.

3. Acute leukemia is essentially a disease of infant and young adult males, but in the fourth decade of life (menopause period), females are more frequently involved.

4. The duration is short. Eighty-four of the 113 cases died within two months after the onset of symptoms clearly due to the leukemia.

5. Acute leukemia of myelogenous origin frequently is diagnosed incorrectly as lymphogenous in type because the primitive bone-marrow cells are mistaken for lymphocytes. Supravital stains aid in distinguishing the type of leukemia.

6. A case with unusual nodules in the stomach mucosa, skin, tongue, and lungs is described.

NOTE.—I wish to express my appreciation of the kindly assistance and criticism given by Dr. George R. Minot, who was my Chief of Service at the time this study was being made.

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#### SYSTEMIC RELAPSES DURING LIVER INDUCED HEMOPOIETIC REMISSIONS IN PERNICIOUS ANEMIA.\*

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PERIODICITY of relapses and remissions is characteristic of many diseases. It is noted in purpura hemorrhagica (thrombopenic), arthritis, malaria, asthuna, hay fever and related diseases, diabetes,

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nephritis, as well as in other conditions. The seasonal recurrence of common colds and bronchitis is a well-established clinical observation. The periodicity in pernicious anemia is an outstanding feature and has been the subject of much study. The relapses in this disease have usually been described as accompanied by changes in the blood. The production of remission by means of liver<sup>1</sup> or an effective liver extract<sup>2,3</sup> has enabled us to throw new light on the nature of this variation as well as of the disease as a whole. The liver-induced remission differs from the spontaneous remission in that the latter is rarely complete, especially in the return of the red blood-cell count to normal. The liver-induced remissions have enabled us to study patients whose blood cell count has reached 5,000,000 red blood-cells per c.mm. and to note what other symptoms and signs have appeared and disappeared with the return of the blood to normal. Previous to this it was often assumed the residual symptoms were the result of the incomplete hematopoietic remission.

Eighty consecutive pernicious anemia patients were studied at this institute, and records were compiled of 304 relapses, of which there was an adequate description. These patients had more relapses, but only those of which definite data was obtainable were included in this study. Of these, 166 recurred in the same season as a previous relapse in the same patient. Thus, if a patient had his first relapse in October and another relapse was in September, October or November, it was classed as in the same season, the term "season" not necessarily referring to winter or summer, but more nearly to the group of months. This means that, although the relapse could have occurred in four possible groups of three months, 54.6 per cent of the relapses occurred in the same group of months. A patient may, then, expect a relapse, or symptoms of it, more frequently in the same group of months as previous relapses have occurred rather than at a new time of the year.

Although the relapses are usually considered as accompanied by a group of symptoms, it has been found that many of these symptoms appear in patients with liver-maintained remissions, even though the blood count remains normal. These patients may show, at intervals, ease of fatigue, glossitis, gastrointestinal symptoms, nausea, loss of appetite, weakness, nervousness, diarrhea, constipation and increase in numbness and tingling of hands and feet. These "abortive relapses" correspond often to relapses on the part of other systems than the blood, and show the inherent tendency of the disease to exacerbations. A loss of appetite during one of these relapses frequently causes a patient to discontinue the liver therapy with the development of a hematopoietic relapse in from four to eight weeks. If liver therapy is not interrupted the symptoms may subside and the blood relapse not appear. The onset of the relapse with loss of appetite may account for the discontinuance of the liver rather than the discontinuance of the liver result in the relapse.

Some patients, however, stop eating liver because they feel perfectly well and do not appreciate the importance of its continuance. These patients may continue for months without a blood relapse. The outstanding feature which has developed from the study of the liver-induced remission is that a remission or a relapse may affect one system and not another, such as the blood and not the nervous system, or the digestive system at another time than the blood. The liver-induced remission is primarily a blood and secondarily a gastrointestinal remission. The loss of appetite may disappear while the patient is taking liver or a liver extract and may also reappear while the blood is normal and while the liver is still being taken. Glossitis may persist or reappear and the achlorhydria does persist. Cutaneous manifestations may improve (decubitus ulcer) or may remain (gray hair). The bone-joint symptoms appear to be entirely independent of the symptoms on the part of other systems. These consist of pains in the joints, stiffness on changing position, pain and tenderness in the bones. There may be an associated atrophic or hypertrophic arthritis. In a relapse one type of symptom may predominate, such as diarrhea, glossitis and abdominal distress. There appears to be no relation between the red blood-cell count and the subjective symptoms. While dyspnea, edema and fatigue may be present with a very low count, they may also be absent while activity is restricted. Some of our patients have been prostrated with a red blood count of 3,000,000 red blood cells per c.mm., whereas others walked about and appeared to show no great discomfort when the red blood count was 1,000,000. Several patients resumed normal activities with a red blood count of 3,000,000, and this apparently was "normal" for them. There is a marked change in subjective symptoms two to three days after liver or liver extract is begun before there is any demonstrable change in the total red blood.

The following types illustrate certain forms of relapses, with and without anemia:

1. **Periodic "Symptomatic" Relapses with "Blood" Relapse.** This is the most commonly described type of relapse, in which the patient tires easily, shows a loss of appetite and a blood study shows anemia. It is quite probable that in many, if not most of these patients, the symptoms precede the anemia. In the average patient, however, the blood is rarely studied when the first symptoms are noticed and a period of weeks to months elapses before the diagnosis is made. This is especially true of the first relapse or the onset, and, unless the patient is followed carefully, is equally true of the subsequent periods.

2. **Periodic "Symptomatic" Relapses, without a Concomitant Change in the Blood Picture.** (a) *When the Blood Count is Normal.*

**Case Reports.** CASE I.—The patient (164077), a woman, aged sixty-one years, had had two relapses previously. In March, 1927, she was in

a relapse and a "liver remission" was induced. She discontinued the liver diet and in November, 1927, developed another relapse. The following data give the subsequent course:

November to December, 1927: "Liver remission."

February, 1928: Tired; not as vigorous as in last month. Red blood cells, 5,100,000 per c.mm.; hemoglobin, 67 per cent. (Sahli.)

March, 1928: Tires easily; loss of appetite. Red blood cells, 4,100,000 per c.mm.; hemoglobin, 69 per cent. (Sahli.)

The ease of fatigue and loss of appetite, although the blood count was within normal limits, were significant as subsequent events showed.

April, 1928: Red blood cells, 3,800,000 per c.mm.; hemoglobin, 67 per cent. (Sahli.)

May, 1928: Not doing well; ease of fatigue; sore tongue. Red blood cells, 3,600,000 per c.mm.; hemoglobin, 81 per cent. (Sahli.)

July, 1928: "Complete" relapse. Red blood cells, 2,800,000 per c.mm.; hemoglobin, 84 per cent. (Sahli.)

August, 1928: "Liver remission." Red blood cells, 4,700,000 per c.mm.; hemoglobin, 91 per cent. (Sahli.)

October, 1928: Appetite lost; tires easily. Red blood cells, 3,500,000 per c.mm.; hemoglobin, 61 per cent. (Sahli.)

In this patient the ease of fatigue and loss of appetite made her disinclined to follow her liver diet or to take liver extract after a remission had been induced and was being maintained. Nevertheless, the symptoms developed while she was taking liver or an effective extract, and she did not have the will power to force the diet at this time.

CASE II.—This patient (170347) illustrates a similar point. After a severe relapse a remission was induced by a liver extract and the patient then ate  $\frac{1}{2}$  pound of liver daily. She felt well and her condition returned to normal and remained so for almost a year, when she lost her appetite. She tried to continue with the liver, but found it impossible. Then she developed weakness, and, with the onset of anemia, showed pallor, dyspnea and palpitation. Neurologic symptoms (difficulty in walking) had developed steadily during the blood remission.

CASE III.—This patient (165879) had a liver remission in April, 1927, and he ate an adequate amount of liver daily. In September his red blood-cell count was 4,250,000 per c.mm., and his hemoglobin was 80 per cent. (Sahli.) At this time he was having progressive difficulty in walking and increased numbness in his legs, symptoms which began a month before. He felt "weak," "dragged out" and was suffering from "gas." During the next three months his blood count remained normal and he received an effective liver extract daily. His neurologic symptoms progressed and the fatigue became more marked, even though his blood count in December was 4,730,000 red blood cells per c.mm. and his hemoglobin 85 per cent. (Sahli.) He became weaker, lost his appetite, discontinued his liver and liver extract (a commercial preparation which proved to be ineffective) which he was taking at that time, and a complete hematologic relapse developed in March, 1928.

*(b) Accentuation of Symptoms of Relapse or the Appearance of New Symptoms when the Blood Count is Practically Stationary, but at a Low Level.*

CASE IV.—(148836.) A woman, aged sixty-one years.

July, 1925: Numbness of hands and feet and weakness.

December, 1925: Burning sensation of hands and feet.

January, 1926: Sore tongue.

April, 1926: Fainting spells.

June, 1926: Lost power to walk. Ankles "gave way."

July, 1926: Lost position sense in her feet and legs.

January, 1927: Loss of control of bladder.

October, 1927: Loss of control of anal sphincter.

December, 1927: Decubitus ulcers.

During this period the blood counts varied between 2,500,000 and 3,500,000 red blood cells per c.mm. The progressive advancement of the spinal-cord lesions accounts for the development of new symptoms in this patient. Subsequently this patient received large doses of an effective liver extract, with improvement in her blood and a lessening in the severity of her neurologic symptoms.

(c) *Symptomatic Relapses during Period of Relative Polycythemia.* Christian<sup>4</sup> pointed out that after a patient had become accustomed to a low red blood-cell count he would have a relative polycythemia when his erythrocyte count reached 5,000,000 per c.mm. The following are some of the symptoms noted in patients when the blood counts became normal. The symptoms were new in some cases, in others they were the reappearance or exacerbation of old ones. Many patients, however, with red blood-cell counts of 5,000,000 or over, experienced no symptoms for months.

TABLE I.—SYMPTOMS NOTED WHEN BLOOD COUNT BECAME NORMAL.

Patient.	Red blood cell count, millions.	Hemoglobin, per cent.	Symptoms.
1 . . . . .	5.98	81	Sore tongue.
2 . . . . .	5.01	82	Sore tongue; dizziness on stooping or turning head rapidly.
3 . . . . .	6.76	85	Nausea; development of "numbness" in fingers.
4 . . . . .	6.06	91	"Peculiar sensation in head."
5 . . . . .	5.60	97	Sensation of warmth and coldness in hands.
6 . . . . .	5.50	77	Sore tongue.
7 . . . . .	5.80	74	Ease of fatigue.
8 . . . . .	5.20	91	Dizziness, palpitation, vertigo.
9 . . . . .	5.02	73	Feeling of fullness in head; dizziness.

3. **Symptomatic Remissions.** While it is not surprising that there should be an alleviation of symptoms when the blood count is normal or nearly so, a remarkable symptomatic improvement appears during the first week of liver therapy, before there is a significant change in the red blood-cell count. A sense of well being appears, a change in mental outlook, a loss of anorexia, nausea and vomiting, improvement in the bowel movements, lessening of ease of fatigue and increase in muscular power (subjective). The psychic "remission" is one of the most marked of any change in medicine. A depressed, apathetic patient, with no appetite, little interest in surroundings and even antagonism to those about him, becomes, within three to five days, a keenly interested person, with

a ravenous longing for food and a cheery mental attitude toward everything. The changes in this respect appear no greater when the red blood count approaches 5,000,000 per c.mm. than when the liver or extracts produce their initial effects during the first few days.

Hunter<sup>5</sup> considered a seasonal periodicity and indicated July, August and September as months of incidence or recurrence; February, March, April, May and June as months of remissions; October, November, December and January as months in which the disease advanced. In Michigan and the surrounding states there appeared to be equal incidence of relapses in all months, with a slight increase in March (spring).

TABLE II.—MONTHS IN WHICH RELAPSES BEGAN.

	Per cent.		Per cent.		Per cent.
January . . .	9.7	May . . .	7.3	September . . .	6.7
February . . .	5.7	June . . .	7.6	October . . .	9.7
March . . .	11.3	July . . .	8.6	November . . .	8.0
April . . .	6.7	August . . .	9.0	December . . .	9.7

**Summary and Conclusions.** 1. In pernicious anemia some of the symptoms of a relapse may occur even though a complete blood remission is maintained with liver treatment.

2. "Abortive relapses" are indicated by loss of appetite, exacerbation of symptoms, or the appearance of new symptoms, when the blood is normal or shows no corresponding change.

3. Liver therapy is often discontinued because of the loss of appetite (gastrointestinal or nervous relapse) and a hemopoietic relapse follows.

4. If the liver therapy is maintained the "abortive relapse" may pass into a remission.

5. Relapses may occur in the part of one or more systems without a corresponding involvement of other systems. (Blood, nervous system, gastrointestinal system, bone-joint system, muscular system.)

6. There is a tendency for relapses to recur in similar seasons of the year (about 50 per cent) and this is also true of the "abortive relapses."

7. The incidence of onset or relapse appears about equally distributed through the year.

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## HEMORRHAGES FROM LACERATIONS OF THE CARDIAC ORIFICE OF THE STOMACH DUE TO VOMITING.

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DURING the past five years we have observed 15 patients who, after a long and intense alcoholic debauch, developed massive gastric hemorrhage with hematemesis. The loss of blood was so great in some of these cases that the patients entered the hospital in circulatory collapse. The characteristic history obtained revealed that after heavy drinking for days or weeks, they experienced persistent nausea, retching and vomiting. Some of the patients had had similar experiences in the past.

The past history and clinical behavior of the patients failed to reveal the source of the hemorrhage. Laboratory tests and careful Roentgen ray studies, undertaken after the bleeding had ceased, were also negative.

The diagnosis of peptic ulcer in the presence of negative findings was not probable. It was obvious that such massive hemorrhages could not be explained by the "alcoholic gastritis." Cirrhosis of the liver was therefore suspected, and although no direct or indirect evidence was obtained for the presence of this disease, it was *assumed* that the source of hemorrhage was a ruptured varix of the esophagus or stomach.

The fact that none of the 15 patients observed showed evidence of cirrhosis of the liver, although 3 of them had had several attacks of hematemesis following alcoholic intoxication, from two to ten years before death, gave rise to the suspicion that the source of bleeding was due to other causes than varices or cirrhosis of the liver. This suspicion was confirmed by the postmortem study of 4 cases, which exhibited strikingly identical lesions at the cardiac opening of the stomach. These consisted of from 2 to 4 definite fissure-like lesions of the mucosa, characteristically arranged around the circumference of the cardiac opening, along the longitudinal axis of the esophagus. The size of the lesions varied from 3 to 20 mm. in length, and from 2 to 3 mm. in width. The edges were raised and slightly thickened, but not indurated. Slight undermining of the edges was occasionally present. In 3 of the cases the lesions were limited entirely

to the stomach, extending almost to the border of the esophagus. In the fourth case the upper quarter of the ulcerations extended into the esophagus. In one of the patients with persistent vomiting no hemorrhage was present at autopsy, but the lesions were identical with those observed in the other 3 patients.

On microscopic section, the lesions were found to be ulcerations of the mucosa, extending as deep as the muscularis. The floor of the ulcers was composed of fresh fibrin and an exudate of polymorphonuclear leukocytes. In some of the sections definitely ruptured arterioles were observed; in others numerous small veins were found in close proximity to the ulcers. Chronic fibrous-tissue reactions were not observed.

Below are presented abstracts of the clinical picture of one of the 11 patients who recovered, and short summaries of the clinical aspects and postmortem findings on 4 patients.

**Report of Cases and the Significance of the Observations.** CASE I.—J. J., a male, white, American real estate dealer, aged fifty-six years, was brought to the hospital because of severe gastric hemorrhage.

For the past twelve years he had had what he called "nervous indigestion." During this time he had marked heartburn and some gnawing pain in the epigastrium. He thought that this occurred one to two hours after meals, but was much worse in the morning before breakfast. At such time he could get relief by inducing vomiting. Bicarbonate of soda also gave him some relief. He had never had a previous hematemesis and had never noticed bloody or tarry stools. There had been no marked loss of weight.

Alcohol always upset his stomach severely and caused him to vomit excessively. He did not drink every day but at different intervals would go off on a spree and drink heavily for several days or a week. After this, digestive symptoms were much worse. His friends seemed to think that his alcoholic indulgence was a little more constant than he would admit. He admitted drinking heavily for the two weeks preceding entrance to the hospital, averaging from a pint to a quart of whisky daily. Eleven days before entrance he had vomited up some blood but in spite of this he continued to drink. He stated that "about an hour before admission he had had a hematemesis of two quarts of blood." Following this he felt very weak and dizzy. He then apparently lost consciousness for a brief period of time but remembers being brought to the hospital.

Physical examination on entrance showed a well-developed and fairly well-nourished middle-aged man. He was rather garrulous and incoherent. There was a strongly detectable alcoholic odor to the breath. The skin and mucous membranes were rather pale but the patient was distinctly not in a condition of shock. The pulse rate was 100, the systolic blood pressure was 130 mm. of Hg., the diastolic 90 mm. On entrance, the red blood-cell count was 3,170,000 per c.mm., the hemoglobin 60 per cent. By the next day the red blood cells had decreased to 2,720,000 per c.mm., and the hemoglobin to 50 per cent. Physical examination was otherwise essentially negative except that the patient showed slightly generalized arteriosclerosis. There were no signs to suggest cirrhosis of the liver or malignancy.

Fluids were restricted and he was given morphia. No further hematemesis occurred. The stools for three days after admission were tarry, but from then on gradually returned to normal. He was started on a Sippy diet two days after admission.

The patient remained in the hospital three and a half weeks. During his stay he had no vomiting or epigastric distress. Three gastric analyses were done. The first two showed an absence of free hydrochloric acid, but in the third it was normal. Before discharge the red blood cell count had returned to 4,500,000 per c.mm., the hemoglobin to 70 per cent. A Roentgen ray examination of the gastrointestinal tract was made a few days before his discharge. It was reported negative except for a slight diaphragmatic hernia.

**DISCHARGE DIAGNOSES.** Alcoholic gastritis. Alcoholism, chronic and acute. Generalized arteriosclerosis. Diaphragmatic hernia.

**CASE II.**—T. K., a male, single, white, longshoreman, aged thirty-five years, during one and a half years had been in the hospital on three different occasions about six months apart because of hematemesis. He first vomited blood ten years ago and had had in all six such experiences. Hematemesis always followed drinking some form of alcohol excessively over a period of from three to four days, and it occurred in the course of subsequent vomiting. No gastrointestinal symptoms had been present except when the patient was drinking. Roentgen ray examination of the gastrointestinal tract two weeks before death was recorded negative. His last hematemesis began about two days before death.

Physical examination the day before death showed that the patient was in a condition of collapse. The liver was palpable 3 cm. below costal margin. Otherwise the examination was essentially negative. The heart sounds were rapid and the pulse feeble. In spite of morphia the patient continued to vomit blood and died about twenty-four hours after entry.

*Autopsy.* (Two hours postmortem.) The body was that of a well-developed, well-nourished, middle-aged white man.

The surfaces of the peritoneal cavity were smooth and glistening. No free fluid was found. The liver edge was 0.5 cm. below the xyphoid and at the costal margin in the midclavicular line.

Pleural and pericardial cavities were negative, and the heart, lungs and spleen essentially normal.

The gastrointestinal tract showed as follows: On opening the cardia of the stomach five narrow fissure-like ulcerations were found distributed around the circumference of the cardia, their upper ends extending into the esophagus. The lesions varied from 10 to 25 mm. in length and 1 to 2 mm. in breadth. They penetrated to the submucosa. The edges were slightly elevated. No bleeding point could be made out. The stomach was empty but the intestines were filled with tarry-black partially-digested blood. No other ulcerations were present and there were no esophageal varices. On microscopic examination these fissures were found to extend down deeply into the submucosa. The floor of the ulcer was covered by an exudation of fibrin and polymorphonuclear leukocytes.

The pancreas was normal, as were the kidneys, adrenals, bladder, aorta and brain.

The liver weighed 1760 gms. Its capsule was smooth. The liver substance was firm and rather reddish-yellow in color. Microscopic examination showed numerous large and small vacuoles in liver cells but no cirrhosis.

*Anatomic Diagnosis.* Ulcerations of cardiac end of stomach with hemorrhage.

**CASE III.**—J. M., male, white, aged thirty-one years, was admitted at 3 A.M. vomiting blood. He had been sick three days at home with nausea, vomiting and epigastric distress. His relatives had noticed that he was very nervous and shaky. At 3 P.M. on the day of admission he began to

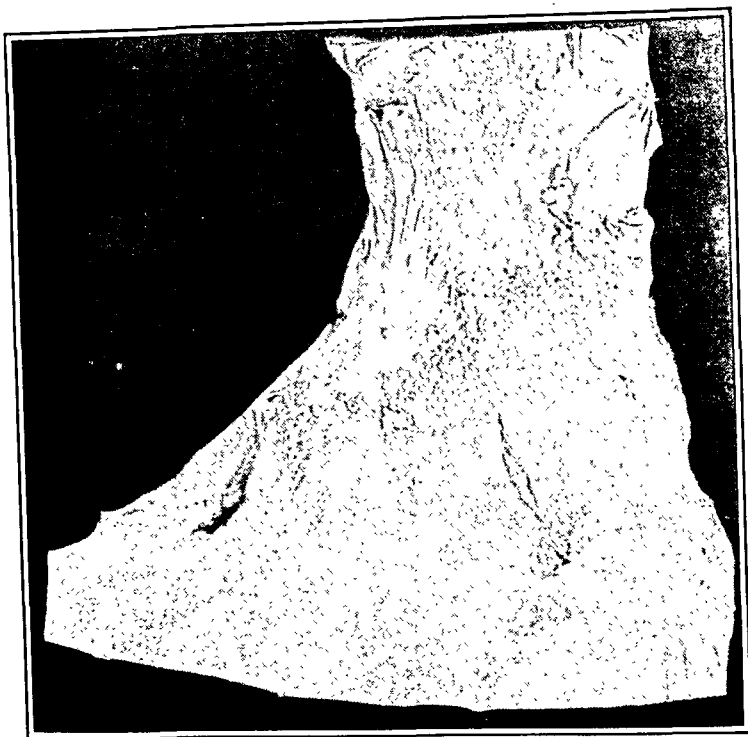


FIG. 1.—Portion of esophagus and cardia of stomach from patient J. F. (Case IV). Just below junction of esophagus and stomach there are two slit-like ulcerations whose axis is the same as that of the esophagus. The two more superficial oval ulcerations at the lower end of right-hand laceration are probably postmortem changes as microscopic examination showed no cellular reaction or fibrin.



FIG. 2.—Microscopic cross section of ulcer on left side of specimen shown in Fig. 1. There is normal stomach mucosa on both sides of ulcer. The edges are elevated. The floor of the ulcer consists of exudate composed of fibrin and polymorphonuclear leukocytes. An arteriole cut more or less longitudinally can be seen just below the ulceration.



FIG. 3.—Arteriole seen in Fig. 2 but taken from another section. Lumen of vessel contains numerous polymorphonuclear leukocytes. At the uppermost portion of the arteriole the wall has ruptured and hemorrhage occurred. The opening has been filled with a plug of fibrin. *Upper front of picture is the floor of ulceration.* Exudation of fibrin and polymorphonuclear leukocytes can be seen.

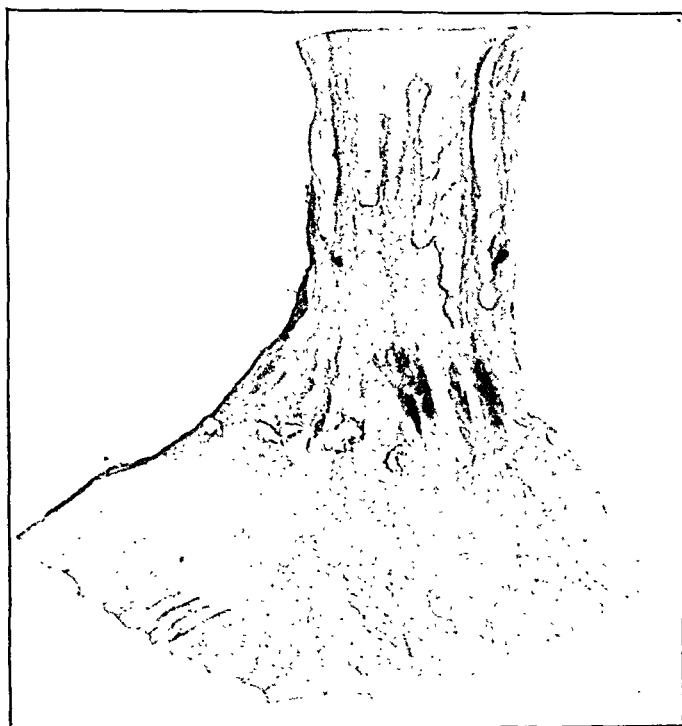


FIG. 4.—Portion of esophagus and cardia of stomach from patient E. F. (Case V). Several fissure-like longitudinal ulcerations can be seen in the first portion of the esophagus. Two are deep, the others rather superficial. There has been complete desquamation of stratified epithelium of the stomach for several centimeters above the juncture of esophagus and stomach.



FIG. 5.—Cross section of one of the ulcerations from Case II from the lower end of the lesion. Normal mucosa of stomach is present on either side of ulceration. Fissure is narrow and extends down into the submucosa. The floor is composed of fibrin and polymorphonuclear leukocytes.



FIG. 6.—Similar to Fig. 5 but taken through the esophageal portion of ulceration. Fibrin and leukocytes can be seen to extend laterally from ulcer into the submucosa.

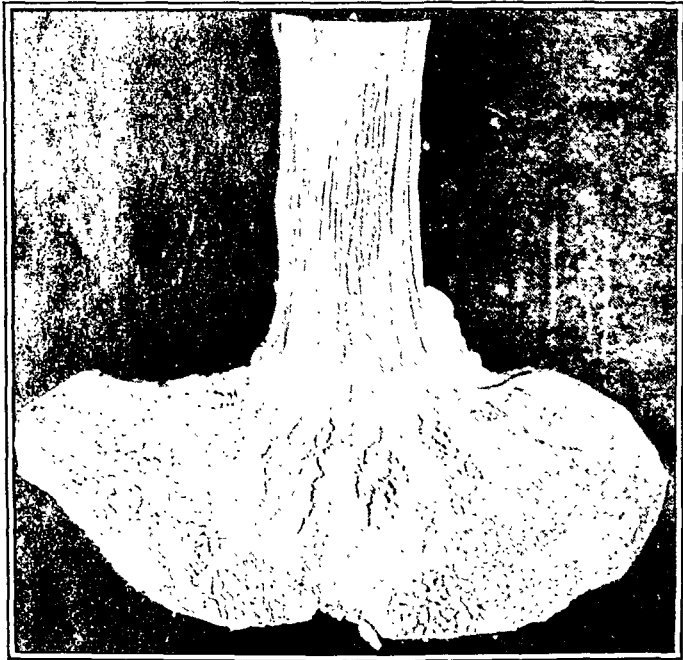


FIG. 7.—Normal esophagus and stomach removed from a child, aged thirteen years, within two hours of death. Numerous rather superficial longitudinal lacerations of the cardia are seen which were produced experimentally by pressure on the stomach after it had been slightly distended with water.

vomit blood profusely and continued to do so until late in the afternoon. The patient's past history was obtained from friends. It revealed that he was a confirmed alcoholic and had been drinking excessively during the past three years.

Physical examination showed a well-nourished, well-developed white man, in a condition of shock. The heart sounds were rapid and feeble, the pulse was of poor quality. There were a few moist râles at both lung bases. Examination was otherwise negative.

The patient continued to vomit small quantities of blood for several hours after admission. The red blood-cell count was 5,690,000 per c.mm., the hemoglobin 60 per cent. When the vomiting ceased the patient's condition did not improve. The pulse rate continued to rise and three days after admission the patient died.

*Clinical Discharge Diagnoses.* Question of cirrhosis of the liver with ruptured esophageal varix, or bleeding gastric ulcer.

*Autopsy.* The body was that of a well-nourished, well-developed young white man.

Peritoneal cavity: The subcutaneous fat was 3 cm. in thickness. No free fluid was observed. The liver edge was 3 cm. above xyphoid and 3 cm. above costal margin; it was of normal appearance. The diaphragm lay at the fourth rib on the right and fifth space on the left.

Pleural cavities: A few fibrous adhesions in left cavity were present.

Pericardial cavity was negative. Heart was normal.

Lungs: The right lung showed nodules of consolidation throughout, and the left showed a similar condition at the base.

The liver was large, flabby, opaque, yellow-red, the surface was smooth. On section markings were indistinct.

Spleen, pancreas, kidneys, adrenals, bladder were normal.

Stomach: At the cardia there were three folds which were definitely associated with ulcerative lesions. The edges were slightly thickened and rose above the ulcers. These were almost linear, the longest measuring 15 mm. in length and 3 mm. in greatest breadth. No diffuse bleeding observed. There was a submucous hemorrhage in the cardia and in the submucosa of the esophagus.

*Anatomic Diagnoses.* Multiple ulcerative lesions of the cardia. Gastric hemorrhage. Terminal bronchopneumonia. Acute dilatation of the right chambers of the heart. Acute passive hyperemia (universal).

CASE IV.—J. F., married, white, male, laborer, aged fifty-six years, was brought to the hospital irrational and mildly delirious. His brother reported that the patient had been a chronic alcoholic for twenty years. Ten years ago he vomited several pints of blood. This recurred about five years ago. Since his last hemorrhage patient had had occasional attacks of epigastric pain associated with nausea and vomiting, which was not related to meals. One week before admission, after a month of excessive drinking, he vomited blood on four occasions. The total amount of this was estimated as about 1½ quarts. Three days before admission he became very restless and irrational.

Physical examination showed a fairly well-developed but poorly nourished middle-aged white man. The conjunctivæ were pale. The pupils were regular and reacted to light and distance. The heart was slightly enlarged, the pulse weak and thready. The abdomen was slightly tender over the epigastrium. The liver dullness appeared diminished by percussion. There was slight twitching of the arms and legs, suggestive of beginning delirium tremens. The systolic blood pressure was 105 mm. of Hg, the diastolic 60 mm. The heart sounds became more rapid and fainter. The patient died within twenty-four hours of admission.



*Autopsy.* (Twelve hours postmortem.) The body was that of a well-developed, well-nourished middle-aged white man.

Peritoneal cavity: Surfaces were smooth and glistening. No free fluid observed. Liver edge was at xyphoid and 2 cm. above costal margin. The diaphragm lay at the fifth rib on both sides.

The heart showed generalized enlargement with dilatation of the right side was noted.

The lungs were negative except for congestion of bases.

The liver was slightly increased in size, the surface smooth and an opaque yellow-red in color, the markings indistinct.

Gastrointestinal tract: Esophagus was negative. The cardia showed two narrow elongated slits in the mucous membrane, measuring 15 mm. by 3 mm. The edges were elevated but not indurated. In the floor of one of these, there appeared to be a ruptured arteriole. Microscopic examination showed this to be the case, and also that the floor of the ulcer was made up of fibrin, red blood cells, and polymorphonuclear leukocytes. The stomach was free from blood but the colon contained a large amount of brown-black pastelike material.

Spleen, pancreas, kidneys, adrenals, bladder were essentially normal.

Brain showed marked edema of the piaarachnoid.

*Anatomic Diagnoses.* Ulcers of the cardiac end of the stomach. Hypertrophy of heart. Minor arteriosclerosis of aorta and coronaries. Acute dilatation of the right heart. Universal acute passive hyperemia. Fatty metamorphosis of liver, kidneys, and heart muscle.

CASE V.—E. G., white, male, American, aged sixty-one years, entered the hospital because of pain in abdomen and constant belching of gas. When at home he never indulged in alcohol, but every two to three months he would drink heavily for three or four days. He had done this for about ten years. For twenty years he had been troubled by belching after eating greasy food. He never had colic or abdominal distress after meals, except after alcoholic excess. For about ten years he had been subject to "dry heaves" after such occasions. This would pass off or be relieved by another drink of liquor. There would be no hematemesis or melena.

One week before entrance, after drinking excessively for several days, he was awakened by sharp abdominal pain which persisted more or less until admission to the hospital. It was located to the left and above the umbilicus and radiated only while belching to the xyphoid. During this time the patient had been unable to hold anything on his stomach, vomiting about two minutes after food was swallowed.

Physical examination showed an emaciated and jaundiced man. Slight dullness was present at the right lung base with diminished breath sounds. The abdomen showed so much tenderness and spasm that palpation was difficult. In the epigastrium a mass was felt by some physicians. The liver edge was palpable at about the level of the umbilicus. There was marked arteriosclerosis.

The urine contained a trace of albumin and numerous brown granular casts. The red blood-cell count was 4,340,000 per c.mm. The hemoglobin was 80 per cent. The icteric index was 70. The van den Bergh test showed a delayed direct and an indirect reaction.

On entrance, the patient did not seem in a serious condition, but four days afterward his color suddenly changed to pale red, his pulse became weak, and he died rather suddenly that night.

*Clinical Diagnoses.* Toxic hepatitis. Carcinoma of head of pancreas. Acute pericarditis. Cholelithiasis and cholecystitis.

*Autopsy.* (Seven hours postmortem.) The skin and mucous membranes were jaundiced.

Peritoneal cavity contained 200 cc. of thin, bright yellow fluid. The liver edge was 6 cm. below the xyphoid and 2 cm. below the costal margin.

Pleural cavities: About 75 cc. of yellow fluid and fibrin present.

The heart was essentially negative.

The lungs showed bronchopneumonia at right base.

Spleen was negative.

Gastrointestinal: Esophagus showed loss of stratified epithelium for about 2 cm. above cardia of stomach. At the juncture of the esophagus and stomach were several fissure-like longitudinal ulcers. Two of these were deep and penetrated to the muscularis. They measured about 10 mm. in length and 2 mm. in thickness. Microscopic section showed the floor of the lesions to be composed of fresh granulation tissue. There was no blood in the stomach or elsewhere in the gastrointestinal tract.

Pancreas was normal.

Liver: Weight 2100 gm. Moderately enlarged. Normal in shape. Capsule thin over a finely-mottled yellow-brown and red surface. Surface very minutely granular in region of gall bladder and near edges of left lobe. Gall bladder and ducts negative.

Kidneys weighed 620 gm. Edge everted on section. Cortex measured 8 mm. Cut surface is gray-red in color.

Adrenals, bladder, genital organs were essentially normal.

*Anatomic Diagnoses.* Acute toxic hepatitis. Bronchopneumonia. Acute nephritis. Ulcerative lesions at the cardiac end of the stomach.

**Discussion.** The identical syndrome presented by these patients suggested that the responsible factor must be either *alcohol*, or *vomiting* or both. That the vomiting, rather than alcohol, played the more important rôle, is supported by the case of an additional patient with pernicious vomiting of pregnancy. In this patient, at autopsy, there was one laceration at the cardiac opening identical with those described above.

Consideration of bodily changes that occur with vomiting also supports the conception that the vomiting is an etiological agent in the production of hematemesis. Vomiting is a complex reflex act composed of a number of highly coördinated bodily changes.<sup>1</sup> During the stage of nausea the pylorus closes and simultaneously the cardia and esophagus dilate. Counter peristalsis then gradually carries the gastric contents into the cardia and esophagus, and at the onset of retching the relaxed diaphragm assumes a deep inspiratory position. With the sudden convulsive increase of intraabdominal and intrathoracic pressure, the gastric contents are then ejected. After repeated attacks of vomiting at short intervals fatigue of the vomiting center sets in and<sup>2</sup> this coördination often becomes disturbed, and simultaneously with the convulsive retching movements the esophagus and diaphragm fail to relax. Thus the gastric contents are thrust with great force against the cardiac opening.

In addition to these pressure changes it may be of etiologic significance that during nausea and vomiting, with closure of the pylorus, the gastric juice accumulates in large quantities in the stomach and is carried by the counter peristalsis toward the relaxed cardia and esophagus. The mucosa over this area may be less

resistant to the *digestive action of the gastric juice* and may consequently become damaged or corroded, especially if other factors such as alcohol and pressure disturbances act synergistically.

In order to ascertain whether such mechanical factors as outlined may play a rôle in the causation of ulcerative lesions of the cardiac opening, we have undertaken to determine *experimentally on the human cadaver* which portion of the mucosa is most sensitive to pressure changes during retching. Two normal stomachs with the esophagus and duodenum attached were removed within two hours of death. The pylorus was tied, and the stomach partially filled with water. Then while putting slight pressure on the esophagus, at about the level at which it passes through the diaphragm, the contents of the stomach were forced into the cardia by squeezing the pylorus. When the condition present during retching is thus imitated, one observes that because of the peculiar shape of the cardia, the narrow cardiac opening greatly dilates. On opening the cardia and the esophagus numerous longitudinal lacerations or tears similar in location and distribution to the lesions found in the cases described were found. The rest of the mucosa is normal. It is highly *plausible*, that in patients reported with persistent vomiting of one or more days' duration, similar pressure conditions may be present.

Ulcerative lesions of the mucosa of the cardiac opening of the stomach, although of rare occurrence as compared with similar lesions of the pylorus, occur nevertheless more often than is recognized. The diagnosis is rendered difficult because the lesions are likely to give less prominent symptoms than ulcers of the pylorus, and Roentgen ray observations, unless performed carefully and with skillful technique, are less helpful than in pyloric lesions. The esophagoscope is the most valuable aid in establishing the diagnosis; and with the recent more widespread use of this instrument, ulcers of the lower portion of the esophagus are more often recognized. Recently, the clinical significance of peptic ulcers of the lower portion of the esophagus is becoming more fully appreciated.<sup>3,4</sup>

Excluding ulcerative lesions of the cardiac opening of the stomach, due to a primary condition, such as new growth, infection, corrosive poison, or developmental abnormality, the most important and frequent lesions are peptic and simple ulcers of unknown etiology. Peptic ulcers of the lower portion of the esophagus and cardia were recognized as early as 1839, by Albers.<sup>5</sup> The existence of the condition was nevertheless doubted until Quincke<sup>6</sup> in 1879 established the entity. Since his description over 100 cases have been reported, but only a small number of these have been proved by autopsy and histologic studies. The structural pathology of the peptic ulcers of the cardia and esophagus are identical with those of the stomach and duodenum. The etiologic factors of peptic ulcer, wherever located, remain obscure.

While peptic ulcers of the cardiac opening may be symptomless, in a considerable number of patients retrosternal pain, or pain over the upper part of the back, is present. If the pain is increased during deglutition the presence of the condition is even more suggestive. In addition, vomiting and dysphagia due to spasm may occur. It is advisable to suspect a peptic ulcer in every case of "cardio-spasm" until proved otherwise. A separation of peptic and acute ulcers of the cardia, without histologic examination, is impossible.

It is characteristic of *acute ulcers* (sometimes called simple ulcers) that *they produce no symptoms until hematemesis* calls attention to their presence. The microscopic structure reveals them to be of recent formation. They consist of a simple loss of mucosa, with occasional damage to the muscularis. An accumulation of fibrin and polymorphonuclear leukocytes takes place, and finally after careful examination a ruptured bloodvessel is detected. Such lesions of the mucosa of the pylorus and the stomach were fully appreciated by such an authority as Rokitsansky.<sup>7</sup>

The occurrence of these acute or simple ulcers close to the cardiac opening was described so vividly by Dieulafoy<sup>8</sup> that following his publication clinicians attributed unexplained gastric hemorrhages to "ulceratio simplex," or to "Dieulafoy's ulcerations."<sup>8</sup> In the first of Dieulafoy's patients a sudden fatal hemorrhage occurred from a superficial "exulceration" "of the size of a five-frank piece," located 2 cm. distal from the cardia. In his second patient the unexpected onset manifested itself in severe hematemesis, which recurred, and during surgical exploration he observed an "exulceration" about the size of a "50-centime piece" near the stomach. In the same year Spiegelberg<sup>9</sup> reported a similar instance occurring in a four days' old baby. At autopsy a pea-sized hemorrhagic area in the mucosa was found at the cardia, in the middle of which was a pinhead-sized superficial ulceration. Since these reports a number of similar cases have been described. In "exulceratio simplex" no etiologic factors can be established and it was suggested by investigators that they might be early stages of peptic ulcers.

We do not believe that our cases are comparable to those of peptic ulcers, or acute simple ulcers described by Dieulafoy and others. A feature of our 4 fatal cases was the gross appearance of the longitudinal fissure-like tears and ulcerations. Histologic examination proved the recent origin of these lesions. The relatively large number of patients who recover spontaneously suggests a strong tendency to healing. Whether the source of bleeding in patients with recurring attacks after repeated alcoholic excess is due to fresh laceration or to the rerupture of vessels in an old lesion cannot be stated with certainty. It is also possible that the lacerations described may lead later to chronic peptic ulcers in some instances.

The conception expressed above that persistent nausea and vomiting—especially if the normal mechanism of the latter is disturbed—is responsible for the lesions of the cardia, is also sup-

ported by 2 of the 3 patients reported by Quincke.<sup>6</sup> Although Quincke's thesis is often quoted as the first proof of the existence of peptic ulcers of the cardia, an analysis of his case reports reveals that only 1 of his 3 patients suffered from peptic ulcer of the esophagus. The condition of his other 2 patients had corresponded exactly to the condition we report upon here. Both were women who vomited intensely and repeatedly before the occurrence of hemorrhage, and in both the diaphragm was pushed upward, due to ascites and metastatic carcinoma in 1 case, and to a huge ovarian cyst in the other. The coördinated mechanism of vomiting was thus interfered with. The lesions found were slitlike tears of the esophagus, involving the mucosa and the muscularis near the cardia. Quincke considered the possibility of vomiting as a cause for the damage, but he discarded this explanation because he had not observed such lesions in other conditions associated with persistent vomiting. It is self-evident that the coördinated changes occurring during vomiting were severely disturbed in these patients, and the condition can be explained by our conception.

In addition to the vomiting, the rôle of alcohol as a predisposing factor cannot be denied. Concentrated ethyl alcohol is a local irritant and an astringent causing temporary or permanent damage to superficial structures. Its rôle in precipitating peptic ulcers was advocated by French clinicians of the nineteenth century.<sup>10,11</sup> The damage to the mucosa of the cardia, where alcohol arrives undiluted from the form in which it is taken, must be greater than on the mucosa of the stomach.

The fact that many patients with most severe and persistent vomiting do not develop gastric hemorrhage does not invalidate our conception of the mechanism of the lesions described. It is seldom that a single etiologic factor precipitates disease. The combined presence of several conditions, some of which are but vaguely recognized, creates pathology in most instances. Persistent retching and vomiting with pressure changes in the stomach, and with the digestive effect of the gastric juice on the mucosa of the cardia, which is probably weakened by the previous damage of alcohol, are the most important causes of the described lacerations and subsequent ulcerations of the cardiac opening of the stomach. The presence of bloodvessels in the lacerated area further determines the severity of the hemorrhage.

**Conclusions.** 1. Severe, occasionally fatal, gastric hemorrhage with hematemesis may occur after periodic alcoholic debauches.

2. Acute lacerations with ulcerations at the cardiac opening of the stomach were the sources of such fatal gastric hemorrhages in three patients here described.

3. Lacerations of the cardiac opening of the stomach leading to massive hemorrhage may also develop in other diseases, for example, pernicious vomiting of pregnancy and malignant neoplasms, if associated with persistent nausea, retching and vomiting.

4. The responsible etiologic factors producing the described lacerations are: pressure changes in the stomach during a disturbed mechanism of vomiting and continuous regurgitation of gastric juice over the mucosa of the cardia. The local irritant and astringent effect of alcohol as well as the nature of vascularity of the mucosa involved are also predisposing factors.

5. In the presence of obscure gastric hemorrhage, or of hematemesis, lesions at the cardiac opening of the stomach should be thought of and in case surgical interference is undertaken the folds of the cardia should be explored carefully.

NOTE.—We are indebted to Dr. Timothy Leary for his kindness in placing at our disposal some of the autopsy material reported in this paper.

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## THE PATHOGENICITY OF YEASTLIKE FUNGI ISOLATED FROM THE HUMAN GASTROINTESTINAL TRACT.

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A LARGE number of yeastlike fungi, which were obtained from the gastrointestinal tracts of normal individuals and of others suffering from various diseases, have been described in a previous paper.<sup>1</sup>

The work reported herein concerns experiments carried out to determine the pathogenicity, for rabbits and guinea pigs, of representative strains of this group of fungi.

The majority of recent work along such lines has been done with strains of *Monilia psilosis*. Ashford<sup>2,3</sup> was able to produce systemic mycosis by intravenous injection into rabbits and guinea pigs of strains isolated from the stools of cases of sprue. The virulence could be enhanced by repeated passage through susceptible animals. Smith<sup>4</sup> obtained somewhat similar results; intravenous injection of monilias from sprue cases, except in very small doses, regularly resulted in septicemia and death of the animal. Moniliasis of the gastrointestinal tract could be produced in guinea pigs by intraperitoneal injection or by introduction through a catheter directly into the stomach. A few of Smith's animals, at autopsy, showed lesions of the gastrointestinal tract. On a diet temporarily deficient in vitamin C, only 2 out of 12 guinea pigs survived. Of the 10, 2 died of septicemia, and the other 8 showed striking and uniform lesions of the tongue, ileum and colon. Intravenous injection into rabbits, on the other hand, of relatively large doses of *Monilia albicans*, obtained from 2 cases of thrush, failed to cause death, although a septicemia with liver lesions could occasionally be demonstrated. Dold,<sup>5</sup> however, failed to attach any significance to the results of parenteral injections in animals as a means of differentiating between the monilias obtained from cases of sprue and those from other sources.

In the literature there are numerous references to single strains of monilias, isolated chiefly from cases of chronic pulmonary or gastrointestinal disease, occasionally from abscesses, and rarely from the blood stream. Many of these produced a fatal septicemia in rabbits on intravenous injection, but any attempt at a comparative biologic classification is impossible. Castellani<sup>6</sup> has isolated a number of different species of monilia from cases of sprue and of diarrhea. Tanner, Lampert and Lampert<sup>7</sup> recovered yeastlike organisms from the throats of 10 per cent of over 1000 normal persons and found that many of these were pathogenic for white mice on intraperitoneal injection.

Considerable work has been reported on feeding experiments with *Monilia psilosis*. Ashford<sup>3</sup> was able to produce stomatitis and diarrhea by feeding strains with enhanced virulence, due to animal passage. Similar lesions were obtained with ordinary strains when the guinea pigs were placed on a vitamin-deficient diet. Smith<sup>4</sup> obtained similar results. Fleisher and Wachowiak<sup>8</sup> fed to rabbits a number of yeastlike organisms isolated from the stools of cases with diarrhea and were able to produce diarrhea and, in some cases, death; occasionally, the fungi were recovered from the blood and from lesions in the internal organs. Wood<sup>9</sup> was able to kill guinea pigs by feeding monilias isolated from cases of pernicious anemia.

The blood of such animals, during life, and the organs, at autopsy, were considered by Wood to show changes comparable to those found in pernicious anemia. No mention was made of the extent of anemia, other than a drop in hemoglobin from 88 to 62 per cent in one instance. He also thought that he found evidences of hemolytic anemia in a rabbit that had received daily intravenous injections of sterile filtrates of dextrose water cultures of such monilias. Browne<sup>10</sup> carried out feeding experiments with rabbits using a strain of *Monilia psilosis* obtained from a typical case of sprue. Three rabbits remained healthy over a period of two months. Of the 6 animals which died, 3 showed a progressive anemia and, at autopsy, marked deposits of blood pigment in various organs. Broun, Jacobson and Garcia<sup>11</sup> and Warthin,<sup>12</sup> using strains from cases of pernicious anemia, have failed to confirm the results of these feeding experiments.

It will be noted that a considerable divergence of opinion exists in regard to the pathogenicity of strains of monilias which are apparently identical. The experiments, herewith reported, were undertaken, primarily, with yeastlike fungi isolated from the stools and gastric contents of cases of pernicious anemia. The macroscopic and microscopic lesions and the symptomatic changes that were observed were compared with those that developed in animals after the injection of similar organisms isolated from cases of disease other than pernicious anemia. The latter included several strains of fungi isolated from "thrush" membranes. All of these strains have been shown<sup>1</sup> to be indistinguishable from representative named strains of *Monilia psilosis*. They have been classified together in the specific group, *Parasaccharomyces A*. Numerous experiments are also reported with representative strains of other specific groups, previously defined.<sup>1</sup>

**Experimental.** No attempt was made to render the animals more susceptible by placing them on a deficient diet. In all experiments, both rabbits and guinea pigs received their usual rations of oats, cabbage, carrots and hay.

**Intravenous Injection. Method.** All strains were grown in dextrose-peptone water at 37.5° C. for approximately forty-eight hours. One or 2 cc. were removed with a sterile pipette and transferred to a test tube. This tube was shaken vigorously for several minutes in order to break up any clumps of the monilia. The culture was then drawn up to the "0.5" mark in a white blood corpuscle counting pipette and diluted with salt solution. After shaking, a counting chamber was filled and the count made. All distinct buds were considered individual organisms. As a rule, the cultures contained approximately 30,000 cells per c.mm., or 30,000,000 ( $30 \times 10^6$ ) per cc. The organisms were injected into the ear vein of a rabbit. The standard rabbit weight was taken as 1800 gm., and the amount of culture for the required dose was calculated from the weight of the rabbit and the count of the culture. If the necessary amount of culture was less than 5 cc., this amount was made to a total volume of 5 cc. with sterile salt solution; if greater than 5 cc., the culture was centrifuged, the clear supernatant fluid



discarded and the sediment diluted to 5 cc. with sterile salt solution. All rabbits that died were autopsied and, in those that failed to show the typical multiple abscesses of the kidneys, portions of these organs were fixed and sectioned in order to demonstrate the presence or absence of microscopic lesions.

The first experiments were carried out with a strain of *Parasaccharomyces* 1, No. 73, isolated from the stool of a case of pernicious anemia. It was found that  $20 \times 10^6$  organisms per 1800 gm. body weight would cause death in a rabbit five or six days following injection. Similar amounts heated at  $60^\circ \text{C}$ . for thirty minutes or amounts less than  $10 \times 10^6$  were invariably innocuous. Death was preceded by a considerable period of inactivity, accompanied, in the majority of instances, by muscular twitchings and, occasionally, by convulsions. There was a marked loss of weight in animals that received a fatal dose. The organisms could be recovered from the blood stream within twenty-four hours after injection. Cultures taken four to six days afterward, however, were invariably sterile, even in fatal cases. Red blood corpuscle counts and hemoglobin determinations failed to reveal any anemia. The injections were usually followed by slight to moderate increases of the white blood corpuscles, even in animals receiving sublethal doses. The reticulocytes showed no significant changes. Urinalysis from rabbits receiving sublethal doses showed the presence of small amounts of albumin and a few granular casts which appeared two or three days following injection and persisted for four or five days; the blood nonprotein nitrogen remained within normal limits. In fatal cases, albumin appeared in the urine on the second or third day, with or without the presence of casts. One or two days before death, there was complete anuria, accompanied by a marked increase in the nonprotein nitrogen of the blood.

At autopsy, in fatal cases, the cortices of the kidneys were invariably riddled with myriads of small pale-yellow abscesses. A few lesions were occasionally found in the pyramids. In rabbits, which received an overwhelming dose, similar lesions, though fewer in number, could be demonstrated in the heart muscle, and, rarely, in the lungs, liver and wall of the intestines. Microscopically, abscesses have been found in the brain and pancreas. Occasional abscesses in the kidney cortices could be demonstrated in animals which had received sublethal doses and had been subsequently sacrificed. Such animals, however, failed to show lesions in other organs.

In sections from rabbits killed within a few hours after injection, it has been possible to show that the kidney lesions start from individual fungi lodged in the capillary network surrounding the convoluted tubules and, occasionally, in the capillaries of the glomeruli. The organisms grow out into the surrounding tubules and glomeruli, polymorphonuclear leukocytes appear, the normal kidney structure is destroyed and the typical miliary abscess results.

The lesions in the pyramids are apparently secondary to the presence of exudate in the collecting tubules. Viable fungi can be recovered from the urine. If the lesions are too few to produce sufficient cortical destruction to result in death, they heal with the formation of scar tissue. In animals which were sacrificed ten days to two weeks following injection and which, grossly and microscopically, showed a moderate number of kidney lesions in various stages of healing, it was impossible to demonstrate the organisms in sections stained by the Gram-Weigert method.

Smears and cultures of the kidneys taken at autopsy in fatal cases were invariably positive. Blood cultures, on the other hand, were always negative.

The accompanying tables (Tables I and II) give abbreviated records of animals which are representative of the group as a whole.

The pathogenicity and lethal dose of various strains of *Parasaccharomyces A* and of strains of other specific and generic groups were also determined by intravenous injections in rabbits. These results are briefly summarized in Table III. It will be seen that all strains of *Parasaccharomyces A*, regardless of their source and age, were able to cause death in amounts ranging from  $2 \times 10^6$  to  $100 \times 10^6$  organisms per 1800 gm. body weight. The macroscopic and microscopic findings were identical with those described following injection with *Parasaccharomyces A*, No. 73. All of the other groups of parasaccharomycetes and representatives of the two other generic groups, however, were apparently innocuous, even with amounts as large as  $100 \times 10^6$ , with the exception of *Parasaccharomyces B*. It should be remembered that the latter species is morphologically indistinguishable, but culturally somewhat different, from *Parasaccharomyces A*. With this organism death did occur with a  $100 \times 10^6$  dose and typical lesions were found. In order to determine whether or not nonfatal kidney lesions were present following injection with fungi from this large group of relatively nonpathogenic strains, rabbits were inoculated intravenously with  $100 \times 10^6$  organisms and sacrificed five days later. All kidneys were grossly negative and abscesses were found microscopically only in the rabbit which received *Parasaccharomyces B*.

All but three of the *Parasaccharomyces A* strains were fatal in numbers ranging from  $2 \times 10^6$  to  $20 \times 10^6$  per 1800 gm. body weight. One of these three strains was obtained from Dr. B. K. Ashford (*Monilia psilosis*, No. 34a) and another from the late Dr. Edwin J. Wood (*Monilia psilosis*, Si.). Although the date of their isolation is unknown, probably both had been kept on artificial media for at least two or three years. The third strain, No. 73, tested twenty-three months following isolation, had a lethal dose of  $100 \times 10^6$ , although a year previous only  $20 \times 10^6$  organisms were necessary to cause death. Ashford's strain was also tested following 3 direct rabbit-blood transfers and it was found that the

TABLE I.—ABBREVIATED PROTOCOLS OF RABBITS INJECTED INTRAVENOUSLY WITH VARYING AMOUNTS OF PARASACCHAROMYCES A, NO. 73.

Day following injection.	Rabbit No. 1. 20 x 10 <sup>6</sup> organisms per 1800 gm. body weight.				Rabbit No. 2. 20 x 10 <sup>6</sup> heat-killed organisms per 1800 gm. body weight.				Rabbit No. 3. 10 x 10 <sup>6</sup> organisms per 1800 gm. body weight.				Rabbit No. 4. 5 x 10 <sup>6</sup> organisms per 1800 gm. body weight.						
	Weight, gm.	R. B. C. x10 <sup>6</sup>	Hgb., per cent	W. C. x10 <sup>3</sup>	Weight, gm.	R. B. C. x10 <sup>6</sup>	Hgb., per cent	W. C. x10 <sup>3</sup>	Weight, gm.	R. B. C. x10 <sup>6</sup>	Hgb., per cent	W. C. x10 <sup>3</sup>	Weight, gm.	R. B. C. x10 <sup>6</sup>	Hgb., per cent	W. C. x10 <sup>3</sup>			
1	1673	4.2	63	27	1625	5.1	67	6	1721	6.2	65	6	2190	5.1	64	12			
2	1555	3.6	56	18	....	...	..	..	1693	6.0	61	11	2092	5.1	57	11			
3	....	...	..	..	....	...	..	..	1540	5.8	61	14	2040	4.9	56	15			
4	1407	3.8	53	35	1505	5.0	67	8	1407	6.2	72	14	2081	5.2	63	16			
5	....	...	..	..	....	...	..	..	....	....	....	....	1855	....	....	....			
6	....	....	....	....	....	....	....	....	1290	Found dead ( <i>fourth day</i> )				1863	....	....	....		
7	1242	Found dead ( <i>fifth day</i> )			....	....	....	....	....	....	....	....	....	....	....	....	....		
8	....	....	....	....	1535	....	....	....	....	....	....	....	....	....	....	....	....		
13	Autopsy, multiple abscesses in kidneys. Iron reaction negative on pieces of liver and kidney.				1505	....	....	....	Marked diarrhea 2 days before death. Autopsy, multiple abscesses in kidneys.										
14					1496	6.1	74	12	....	....	....	....	....	....	....	....	....	....	....
19					....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
					Survived								Survived						

TABLE II.—URINARY AND BLOOD-NITROGEN FINDINGS IN RABBITS FOLLOWING FATAL AND NONFATAL DOSES OF PARASACCHAROMYCES A.

Days before or following injection.	Rabbit No. 9. 10 x 10 <sup>6</sup> organisms from 24-hour culture of <i>Parasaccharomyces A</i> , No. 73, injected intravenously.										Rabbit No. 10. 20 x 10 <sup>6</sup> organisms from 24-hour culture of <i>Parasaccharomyces A</i> , No. 73, injected intravenously.									
	Urine.					Blood N. P. N., mg. per 100 cc.	Weight, gm.	Urine.					Blood N. P. N., mg. per 100 cc.							
	Amount, cc.	Reac- tion.	Specific gravity.	Albumin.	Sedi- ment.			Amount, cc.	Reac- tion.	Specific gravity.	Albumin.	Sedi- ment.								
2	2067	320	Alk.	1.008	0	Neg.	36.7	2449	320	Alk.	1.014	0	Neg.	30.7						
1	1968	150	Alk.	1.018	0	Neg.	....	2417	410	Alk.	1.010	0	Neg.	....						
	2037	290	Alk.	1.015	0	Neg.	....	2412	470	Alk.	1.012	0	Neg.	....						
1	....	180	Alk.	1.015	0	Neg.	....	....	260	Alk.	1.014	0	Neg.	....						
2	1870	180	Alk.	1.015	S. P. T.	Neg.	....	2202	110	Alk.	1.012	S. P. T.	Neg.	....						
3	1875	100	Alk.	1.022	0	Neg.	....	2145	110	Alk.	1.018	L. T.	Neg.	....						
4	1860	37	Str. alk.	1.025	T.	Occ. gran. cast	40.0	2117	0	...	....	....	....	131.8						
5	1827	115	Str. alk.	1.018	S. P. T.	Occ. gran. cast	....	2045	0	Found dead										
6	1802	300	Alk.	1.017	S. P. T.	Occ. gran. cast	....	Autopsy—generalized multiple abscesses.												
7	1757	55	Alk.	1.025	0	Neg.	....													
8	1818	Survived					41.0													

Autopsy—generalized multiple abscesses.

Survived

Found dead

TABLE III.—SUMMARY OF RESULTS FOLLOWING THE INTRAVENOUS INJECTION INTO RABBITS OF KNOWN DOSES OF VARIOUS YEASTLIKE FUNGI.

Classification of the fungus.	Strain.	Source.	Clinical diagnosis.	Age of culture.	Intravenous dose— $\times 10^6$ organisms per 1800 gm. body weight.						
					1	2	5	10	20	40	100
Parasaccharomyces A	No. 4	Stool	Pernicious anemia	13 mos. 24 mos.	S D 8	D 3	D 5 D 7	D 4 D 4	D 3 D 4		
Parasaccharomyces A	No. 73	Stool	Pernicious anemia	11 mos.	S			S	D 5 D 9	D 7	
Parasaccharomyces A	No. 31a	Stool	Typhoid fever	23 mos.			S		S	S	D 5
Parasaccharomyces A	No. 39	Stool	Congenital heart disease	14 mos. 14 mos. 25 mos.			D 12 D 8	D 5 D 5	D 7 D 5		
Monilia psilosis	No. 34a	Stool	Sprue	3 rabbit transfers				S	S	S	D 7
Monilia psilosis	Si.	Stool	? Sprue	? transfers				S	S	D 8	
Parasaccharomyces A	B-14-16	Throat	Thrush	1 mos.				S	S	D 7	D 5
Parasaccharomyces A	B-26-2541	Throat	Thrush	5 mos.			S	D 5	D 5	D 3	
Parasaccharomyces A	U-26-37	Esophagus	Severe malnutrition (autopsy)	3 mos.	S		D 5	D 8	D 4	D 3	
Parasaccharomyces B	No. 130	Gastric contents	Pernicious anemia	22 mos.						S	S
Parasaccharomyces C	No. 67	Gastric contents	Chronic nephritis	22 mos.							D 15
Parasaccharomyces D	No. 18	Stool	Pernicious anemia	22 mos.					S		S
Parasaccharomyces E	No. 106	Stool	Hysteria	22 mos.					S		S
? Parasaccharomyces I	No. 31b	Stool	Typhoid fever	23 mos.						S	S
Cryptococcus A	No. 16b	Gastric contents	Carcinoma of stomach	24 mos.						S	S
Endomyces A	No. 123	Stool	No disease	21 mos.						S	S

S = survived D = died (number = day following injection) with bold-face type indicating minimal lethal dose.

lethal dose had been reduced from  $100 \times 10^6$  to  $40 \times 10^6$  organisms. These results would seem to indicate that the virulence diminishes with the age of culture. One strain, *Parasaccharomyces A*, No. 4, however, which, incidentally, had the lowest lethal dose, retained its original virulence even after two years on artificial media. Furthermore, the lethal doses of fairly recently isolated "thrush" strains were practically of the same magnitude as those of intestinal strains which had been kept on artificial media for more than a year.

**Intraperitoneal Injection.** Rabbits were injected intraperitoneally with known amounts of two strains of *Parasaccharomyces A*, No. 4 and No. 73, both isolated from cases of pernicious anemia. With the former,  $200 \times 10^6$  organisms per 1800 gm. body weight, or 100 times the fatal intravenous dose, were required to cause death, which occurred in five days. With the latter,  $650 \times 10^6$  organisms, or 30 times the fatal intravenous dose, caused no apparent ill effects, whereas  $500 \times 10^6$  organisms, injected intraperitoneally two weeks following the first injection, caused death in twenty-four hours. At autopsy the outstanding lesion, in both instances, was a marked fibrinous peritonitis; a few abscesses were found in the kidneys and liver, but they apparently had arisen from subcapsular infection. In spite of the massive doses received, there was no evidence of invasion, with subsequent blood-stream infection. In animals that received sublethal doses there was a steady increase in body weight over a period of two or three weeks and the blood picture remained normal.

A series of 38 guinea pigs, weighing approximately 300 gm. each, was injected intraperitoneally with  $250 \times 10^6$  organisms from four-day dextrose peptone water cultures of 38 different strains. From half of these animals satisfactory stool cultures were obtained prior to injection—8 were negative for yeastlike fungi, 10 yielded organisms similar to *Parasaccharomyces C* and one a strain similar to *Parasaccharomyces A*. The animals were weighed and their stools cultured at two-, four- and nine-week intervals. Only 4 of the guinea pigs showed organisms in the stools similar to those injected—3 of these showed no ill effects from the injections and were discarded at the end of two months; the other, which died after four and a half weeks, showed no lesions, at autopsy, which could be attributed to the fungi. Of the 38 guinea pigs, 24 died after periods ranging from four days to nine and a half weeks—unfortunately all of the guinea pigs were, at that time, going through a serious epidemic of pneumonia. Of these 24 animals, 9 showed, at autopsy, unilateral or bilateral pneumonia, 14 no demonstrable lethal lesions, and one a purulent peritonitis. The latter animal died four days after the injection of *Parasaccharomyces A*, No. 4, which strain, it will be recalled, was found to be relatively virulent for rabbits. In this one instance, death was apparently due to the fungi. Cultures taken of the hearts' blood of the autopsied animals were consistently negative.

Tiny subcutaneous abscesses at the site of injection and localized peritonitis, particularly in the neighborhood of the pancreas, with or without small abscesses, were frequently observed and cultures from such abscesses usually yielded yeastlike fungi. Sections of the organs examined microscopically showed no evidence of a generalized infection and Gram-Weigert stained sections of the pneumonic lungs were negative for fungi.

Several guinea pigs were injected intraperitoneally with increasing amounts, up to 5 cc., of four- and seven-day Berkefeld filtrates of *Parasaccharomyces A*, No. 73, cultures in dextrose peptone water. No ill effects were noted.

**Intradermal Injection.** Rabbits and guinea pigs were injected intradermally with four- and seven-day Berkefeld filtrates of *Parasaccharomyces A*, No. 73, cultures in dextrose peptone water. The skin reactions were consistently negative.

**Feeding.** Three guinea pigs were fed cultures of three different strains of *Parasaccharomyces A* (*Monilia psilosis*, No. 6 and *Parasaccharomyces A*, No. 73 and No. 131) for a period of one month. Three cubic centimeters of a twenty-four-hour dextrose peptone water culture were fed daily by mixing with chopped cabbage and carrots. As will be seen from Table IV, the animals gained steadily in weight and the blood pictures remained essentially normal. They were killed at the end of a month. There were no gross lesions and portions of the livers, kidneys and spleens failed to give any test for hemosiderin. The organisms were recovered on culture from the intestinal tract.

**Discussion.** In an earlier paper<sup>1</sup> it was emphasized that the majority of yeastlike fungi isolated in appreciable numbers from human stools and gastric contents, particularly the former, are morphologically and culturally identical. These organisms were all included in the specific group, *Parasaccharomyces A*. In this group, also, were placed various named species of monilia and yeastlike organisms obtained from typical "thrush" membranes. This specific identity is further substantiated by the pathogenicity of various strains, regardless of their source, when injected intravenously, in fairly large numbers, in rabbits. The difference, as regards pathogenicity, between *Parasaccharomyces A* and the other groups of parasaccharomycetes is striking. Only one other group, *Parasaccharomyces B*, was able to produce lesions, even in relatively large amounts. This group morphologically, and, in certain respects, culturally, is identical to *Parasaccharomyces A*. Representatives of the two other generic groups, cryptococci and endomycetes, were harmless.

These findings would seem to indicate that, in judging whether or not a certain yeastlike fungus is "pathogenic," but little significance can be attached to the fact that it is able to cause death when injected intravenously in a rabbit. Such a strain would probably fall into the large specific group, *Parasaccharomyces A*, but repre-

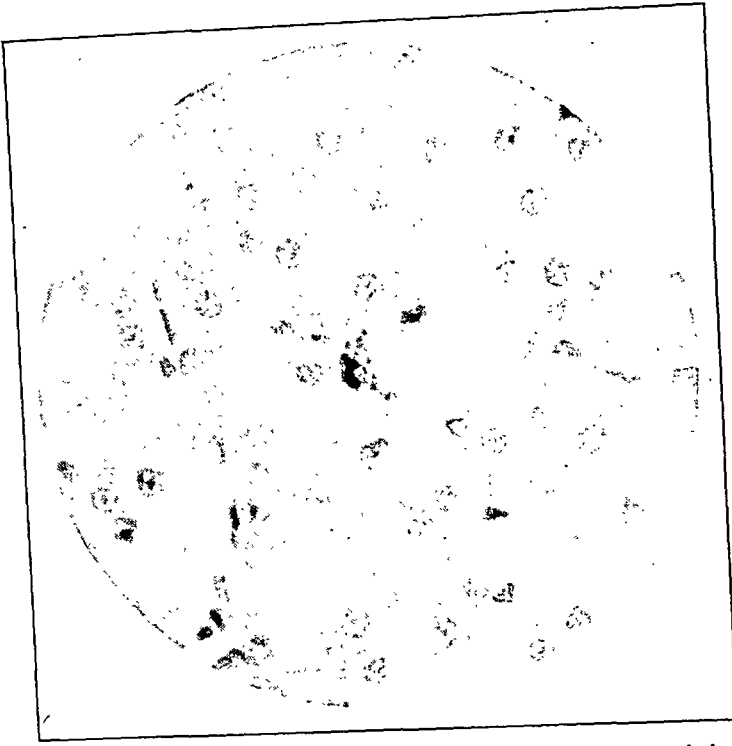


FIG. 1.—Rabbit No. 508, killed five hours after the intravenous injection of  $50 \times 10^6$  *Parasaccharomyces A.* Section of kidney, Gram-Weigert stain.  $\times 1000$ . In the center of the field is a single organism, located in an intertubular capillary.

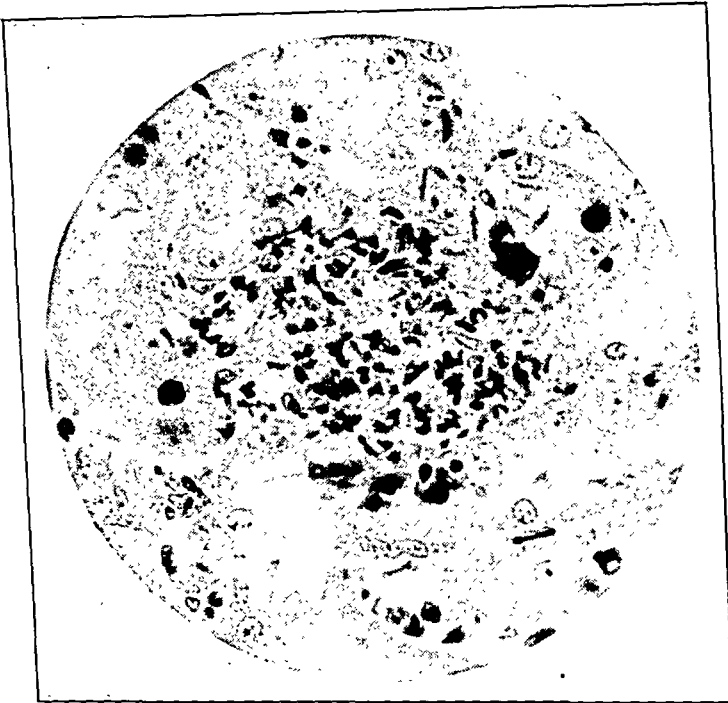


FIG. 2.—Rabbit No. 507, killed twenty-three hours after the intravenous injection of  $50 \times 10^6$  *Parasaccharomyces A.* Section of kidney, eosin and methylene blue stain.  $\times 700$ . The lesion is more advanced. Several tubules are involved and there is a definite focus of acute inflammation. Numerous elongated forms of the fungus can be seen in the lumen of the convoluted tubule in the upper half of the field.



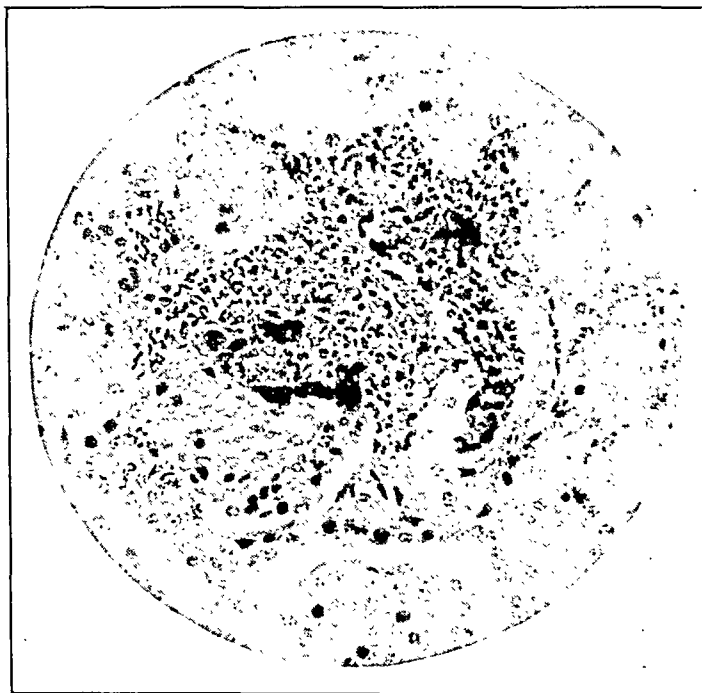


FIG. 3.—Rabbit No. 507, killed twenty-three hours after the intravenous injection of  $50 \times 10^6$  *Parasaccharomyces A.* Section of kidney, eosin and methylene-blue stain.  $\times 500$ . This lesion involves a glomerulus. The acute inflammatory exudate can be seen in the glomerular tuft and capsule, in the surrounding kidney tissue, and in the lumen of an adjacent convoluted tubule.

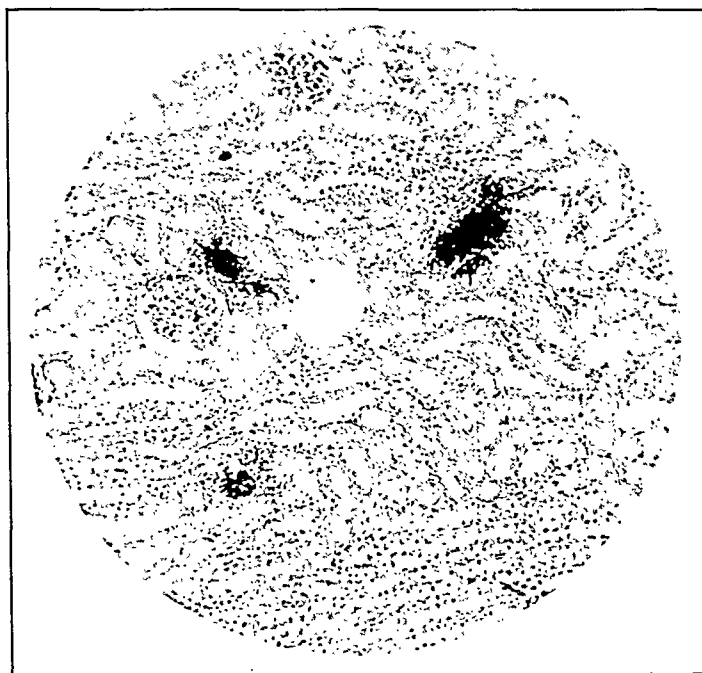


FIG. 4.—Rabbit No. 507, killed twenty-three hours after the intravenous injection of  $50 \times 10^6$  *Parasaccharomyces A.* Section of kidney, Gram-Weigert stain.  $\times 160$ . A lower magnification showing lesions similar to the two preceding, but stained in such a way as to bring out the colonies of fungi.

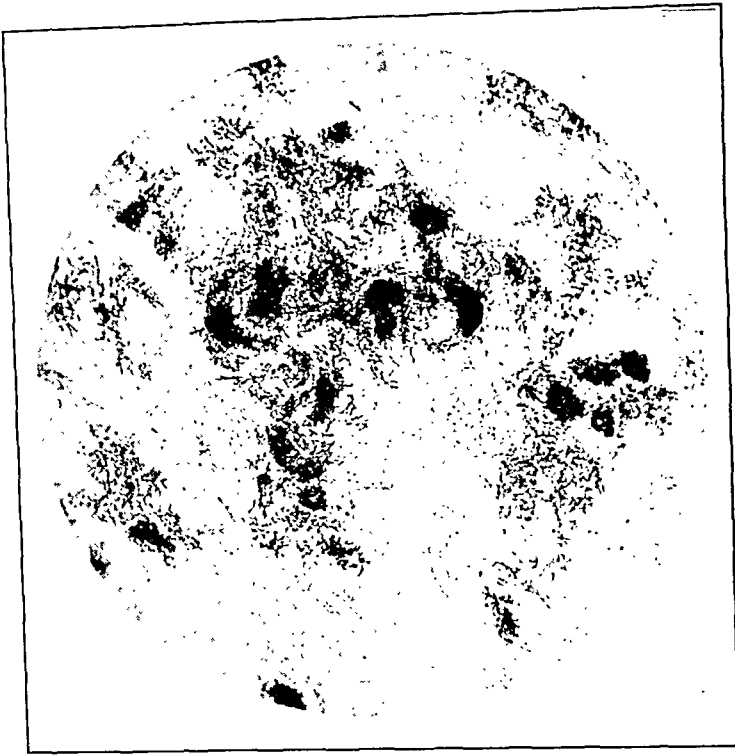


FIG. 5.—Rabbit No. 120, found dead four days after the intravenous injection of  $40 \times 10^6$  *Parasaccharomyces A.* Section of kidney, Gram-Weigert stain.  $\times 125$ . An atypical reaction, in that there are an enormous number of organisms with very little inflammatory reaction. The large compact masses are contained in the dilated lumina of convoluted tubules.

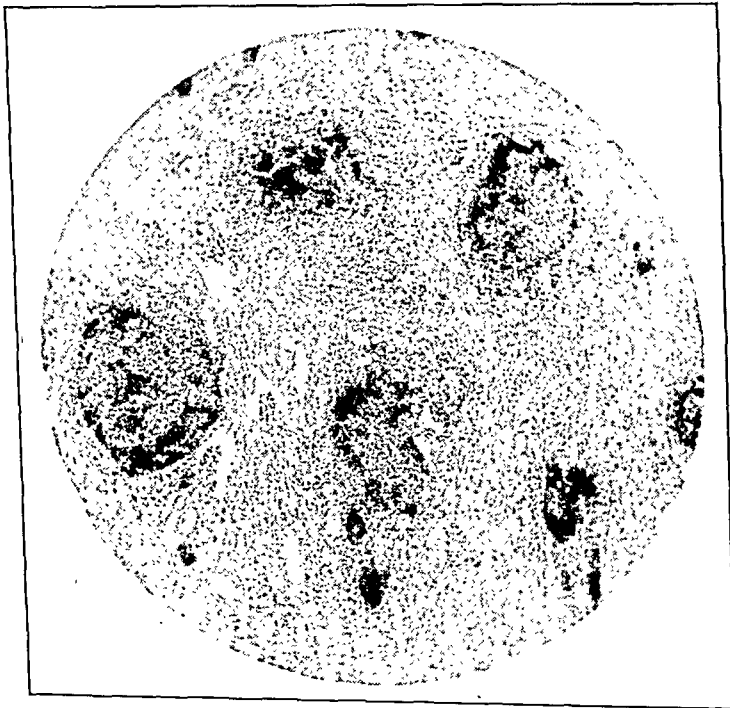


FIG. 6.—Rabbit No. 25-1, found dead five days after the intravenous injection of about  $20 \times 10^6$  *Parasaccharomyces A.* Section of kidney, eosin and methylene-blue stain.  $\times 100$ . Advanced lesions showing definite abscess formation with extensive destruction of kidney tissue.



TABLE IV.—PROTOCOLS OF GUINEA PIGS THAT RECEIVED DAILY FEEDINGS OF FRESH CULTURES OF DIFFERENT STRAINS OF *PARASACCHAROMYCES A.*

Days after feeding began.	Guinea pig No. 1. <i>Parasaccharomyces A.</i> , No. 131.					Guinea pig No. 2. <i>Parasaccharomyces A.</i> , No. 73.					Guinea pig No. 3. <i>Monilia psiloxis</i> , No. 6.				
	Wt., gm.	R. B. C. $\times 10^6$	Hgb., per cent.	W. B. C. $\times 10^3$	Wt., gm.	R. B. C. $\times 10^6$	Hgb., per cent.	W. B. C. $\times 10^3$	Wt., gm.	R. B. C. $\times 10^6$	Hgb., per cent.	W. B. C. $\times 10^3$	Wt., gm.	R. B. C. $\times 10^6$	Hgb., per cent.
1	380	5.4	74	22	377	5.5	77	13	393	5.9	78	11	393	5.9	78
3	391	...	...	...	401	...	...	...	386	...	...	...	386	...	...
6	374	5.9	77	20	365	6.2	75	15	374	6.5	83	14	374	6.5	83
11	400	...	...	...	410	...	...	...	388	...	...	...	388	...	...
13	410	...	...	...	408	...	...	...	384	...	...	...	384	...	...
16	372	...	...	...	376	...	...	...	368	...	...	...	368	...	...
20	407	5.8	65	19	395	5.8	76	17	387	4.8	63	13	387	4.8	63
22	394	...	...	...	394	...	...	...	384	...	...	...	384	...	...
23	422	...	...	...	415	...	...	...	417	...	...	...	417	...	...
24	...	5.4	72	15	...	5.5	71	17	...	5.9	68	15	...	5.9	68
27	430	...	...	...	409	...	...	...	...	...	...	...	...	...	...
27	423	...	...	...	419	...	...	...	421	...	...	...	421	...	...
30	447	4.9	63	14	434	5.6	75	15	445	5.2	68	10	445	5.2	68

All 3 guinea pigs were killed on the thirtieth day. Autopsies, no gross or microscopic lesions, negative tests for hemosiderin on pieces of livers, kidneys and spleens, yeastlike organisms, morphologically and culturally identical with those fed, were recovered in each instance from the intestinal contents.

sentatives of this group have been recovered from the stools and gastric contents in a wide variety of conditions where there was no indication of abnormality in the gastrointestinal tract.

The nonpathogenicity of the other specific and generic groups is in accord with the findings of many other investigators when working with cultures of "wild yeasts." The criterion by virtue of which the term "wild yeast" is applied is somewhat doubtful, but it would seem, in general, that the adjective "wild" is applied to any yeastlike organism which is nonpathogenic to the rabbit on intravenous injection. No hint has been obtained as to the fate of these non-pathogenic strains in the rabbit.

The pathologic findings in the organs, particularly the kidneys, of rabbits that had been sacrificed or had succumbed following the intravenous injection of *Parasaccharomyces A* were extremely interesting. The typical miliary abscesses, except after overwhelming doses, were found almost exclusively in the cortices of the kidneys, in spite of the fact that individual fungi could be demonstrated in the capillaries of the lungs, liver, spleen, and heart muscle an hour after injection. It would seem likely that this particular portion of the kidneys offers a more favorable site for the growth of the fungi, possibly on account of better conditions of hydrogen-ion concentration or of nutrition. From their original location in the intertubular capillaries and, more rarely, those of the glomeruli the organisms proceed to multiply and to invade the contiguous tissue; and, an abscess results. Death, in such cases, would appear to result primarily from extensive kidney damage, for it is preceded by complete anuria, a marked increase in blood nonprotein nitrogen, collapse and, frequently, muscular twitchings and convulsions. When large numbers of the organisms were injected, abscesses were found in other parts of the body. Gastrointestinal lesions were never found except in animals that had received an overwhelming dose and, in such cases, the lesions consisted of abscesses identical with those found in practically every organ of the body. Diarrhea was sometimes present in fatal cases, but was not a consistent finding. The rabbits showed no striking change in the blood picture and the organs at autopsy, failed to give an iron reaction indicative of liberation of abnormal amounts of hemoglobin-derived pigments.

In a series of guinea pigs, that received large intraperitoneal doses, the animals did not die of lesions that could be attributed to fungus infection, with one exception, and this one died very acutely with a marked purulent peritonitis. It is true that the results might have been different, if the animals had been placed on particular diets deficient in one or more vitamins, minerals, or other substances.

Even though it is accepted that *Parasaccharomyces A* is pathogenic for rabbits, it must be acknowledged that the virulence is exceedingly low and that the fatal lesion is quite unusual. A considerable number of organisms must be injected intravenously in order to produce

death. Sublethal doses cause a varying number of abscesses in the kidneys, but these lesions are quickly mastered by local or circulating protective factors and subsequent systemic infection never occurs. Even in fatal cases, fungi were never recovered from the hearts' blood provided a period of two days had elapsed since the last injection. This lack of invasive power is also clearly demonstrated by the observations on rabbits that received intraperitoneal injections. In one instance, 100 times the lethal intravenous dose was required to produce death; and, even then, there was no evidence, macroscopically or microscopically, of blood-stream infection. The pathologic findings, following intravenous injection, seem to be directly proportional to the number of organisms injected. With sublethal and minimal lethal amounts, the lesions were confined, practically entirely, to the kidneys, but, as the dose was increased, more organs were found to be involved.

Guinea pigs fed normal diets containing cultures of *Parasaccharomyces A* failed to show any ill effects. The gain in body weight was progressive and there was no evidence of anemia.

The evidence accumulated in the work reported here and in the previous paper<sup>1</sup> would seem to warrant the conclusions that the yeastlike fungi occur quite commonly in the human gastrointestinal tract and that, with the exception of *Parasaccharomyces A*, they are essentially saprophytic. That this one species is relatively parasitic is evidenced by the fact that it is about the only one to be recovered in appreciable numbers from human stools. If animals are injected with sufficient numbers of a strain of *Parasaccharomyces A*, intravenously or intraperitoneally, or, if, as other investigators have shown, the normal protective agencies are diminished by certain vitamin-deficient diets, lesions result and death ensues. The parallel of the latter condition exists in the human body, for it is a well-known fact that in the one condition, "thrush," in which the etiologic factor is undoubtedly a *parasaccharomyces* and probably one belonging to the specific group, *Parasaccharomyces A*, a state of lowered resistance in the patient is usually a pre-requisite. Thrush membranes, as stated by Osler,<sup>13</sup> most commonly occur "in enfeebled, emaciated infants with digestive or intestinal troubles" and "in adults in the final stages of fever, in chronic tuberculosis, diabetes, and in cachectic states." There are undoubtedly authentic cases in which death has been due to a generalized infection with these organisms. In such cases, however, there was probably some underlying cause which permitted the invasion and multiplication of the fungus. The same holds true for other common relatively nonpathogenic inhabitants of the gastrointestinal tract—for instance, *Bacillus proteus*.

**Conclusions.** 1. Yeastlike fungi belonging to the specific group, *Parasaccharomyces A*, regardless of their source, are pathogenic for rabbits following intravenous injection.

2. Representative strains of other specific and generic groups of yeastlike fungi, isolated from the gastrointestinal tract, are non-

pathogenic, at least when injected intravenously in rabbits in large doses.

3. Relatively large doses of *Parasaccharomyces A* are necessary to cause death in rabbits and the invasive power of such organisms, as judged by observations on animals following intraperitoneal injection, is practically nil.

4. Death in rabbits following the intravenous injection of *Parasaccharomyces A* is due, primarily, to extensive renal damage, with a resulting uremia.

5. No gastrointestinal lesions or noteworthy changes in blood picture were observed in guinea pigs fed for a month with fresh cultures of *Parasaccharomyces A* in addition to a normal diet.

6. These facts, together with others previously reported, seem to warrant the conclusions that the yeastlike fungi classified as *Parasaccharomyces A* are relatively common in the human gastrointestinal tract and that their importance in human pathology rests in their possible rôle as infectious agents in conditions of lowered resistance.

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#### THE CEREBRAL CIRCULATION.

#### IX. THE RELATIONSHIP OF THE CERVICAL SYMPATHETIC NERVES TO CEREBRAL BLOOD SUPPLY.\*

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FOR more than thirty years there has been a controversy as to whether or not cerebral vessels are under vasomotor control. This paper is an attempt to indicate briefly the history of the subject and

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to report in a summary way some recent work\* from the Department of Neuropathology at the Harvard Medical School.†

The standard textbooks on physiology in English give the impression that the question is settled: that there is no such control, and, in fact, that there are no nerves to the vessels of the brain. For example, Bayliss (1924)<sup>1</sup> states: "As will be seen later, there is no adequate evidence that the cerebral vessels have any vasomotor control; the importance of the brain is such that its circulation is regulated by the whole of the rest of the body, which is caused to accommodate itself, by constrictor and dilator nerves, to the needs of the brain." On the other hand, clinicians have long accepted "cerebral vascular spasm" as the cause of transient hemiplegia, aphasia, migraine and convulsion. For example, we find in "Cecil's Textbook of Medicine" (1927):<sup>2</sup> "There have been reported cases of transitory hemiplegia resulting from *cerebral vascular spasm*. The condition is allied to intermittent claudication of the lower extremities. These 'vascular crises,' as they have been termed by Pal, are particularly common in smokers."

The physiological dogma that the cerebral vessels lack all vasomotor control seems to have its origin in the work of Leonard Hill (1896).<sup>3</sup> Hill's experiments led him to conclude that in every experimental condition the cerebral circulation passively follows the changes in the general arterial and venous pressures, and that there is no evidence for the causation of cerebral anemia by spasm of the cerebral arteries. These sweeping conclusions have been accepted without critical examination by the writers of most textbooks. The work of Weber (1908)<sup>4</sup> does not appear to have been read by many English-speaking physiologists. Experimenting with cats, he found in 75 per cent a decrease in brain volume following stimulation of the cervical sympathetic. He criticized Hill's method because it did not take into account changes in pressure due to an increase in the amount of cerebrospinal fluid, a factor which might well mask the effects of vascular change as determined by Hill. He, therefore, considered Hill's method inadequate and his conclusions false. Weber's work, though excellently done, gives only indirect evidence. The vessels of the brain were not actually seen to change in caliber;

\* For a detailed discussion see Lennox and Cobb.<sup>23</sup>

† The individual studies are as follows: Observation and Measurement of Pial Vessels: H. S. Forbes, Arch. Neurol. and Psychiat., 1928, 19, 751. A Quantitative Study of Cerebral Capillaries: S. Cobb and J. H. Talbott, Trans. Assn. Am. Phys., 1927, 42, 255. The Vasomotor Control of Cerebral Vessels: H. S. Forbes and H. G. Wolff, Arch. Neurol. and Psychiat., 1928, 19, 1057. The Action of Hypertonic Solutions—Part I: H. G. Wolff and H. S. Forbes, Arch. Neurol. and Psychiat., 1928, 20, 73. Observations of the Pial Circulation during Changes in Intracranial Pressure, H. G. Wolfe and H. S. Forbes, Arch. Neurol. and Psychiat., 1928, 20, 1035. Velocity of Intracranial Blood Flow: H. G. Wolff and H. Blumgart, 1928, Arch. Neurol. and Psychiat., 21, 795. Changes in Cerebral Capillary Bed following Cervical Sympathectomy: J. H. Talbott, H. G. Wolff and S. Cobb, 1929, Arch. Neurol. and Psychiat. (in press). Quantitative Study of the Capillaries in the Hippocampus: S. Cobb, Arch. Surg., 1929, 18, 1200.



he argued that they must contract and dilate because brain volume changed and all other variables were controlled.

Müller and Siebeck (1907)<sup>5</sup> carried out experiments which indicated that there was a distinct and fairly rapid increase in the volume of the brain after section of the cervical sympathetic, the systemic blood pressure remaining at a constant level. Hürthle (1889)<sup>6</sup> and others in his time measured the pressure in the circle of Willis. Stimulation of the cervical sympathetic nerves caused an increased arterial pressure synchronous with a drop in jugular venous pressure. For a comprehensive bibliography, the reader is referred to Tigerstedt's *Physiologie des Kreislaufes* (1923)<sup>7</sup> and to the recent paper by Forbes and Wolff (1928).<sup>8</sup>

A series of experiments by Talbott, Wolff and Cobb (1928),<sup>9</sup> that have not yet been published, may be briefly reported here. Ten cats were operated upon under ether anesthesia. In each the left cervical sympathetic nerve was aseptically exposed, cut and approximately 2 cm. removed. An increase in temperature of the ear and a constriction of the pupil on the operated side was accepted as evidence that the cervical sympathetic nerve had been cut. After a lapse of time varying from one hour to six days, the vessels of the head and brain were injected with a 2 per cent aqueous solution of Berlin blue. The injection method is briefly as follows:

After anesthetization with ether the thorax was rapidly opened and the heart and great vessels were exposed. The internal mammary arteries and the abdominal aorta were clamped. The pericardial sac was next opened and an incision was made through the wall of the left ventricle. A cannula was inserted through the incision and carried past the aortic valves into the ascending aorta and ligatured. The injection mass, warmed to body temperature, was then allowed to run in at a constant pressure varying between 220 and 225 mm. of mercury. Ludwig's injection apparatus was used. With this apparatus the injection pressure was recorded and controlled throughout each experiment. The amount of Berlin blue injected into each animal varied between 150 and 200 cc. The injection was started while the animal was still alive, but within five to ten seconds the animal was dead. Speed is an important factor because even a brief delay would allow asphyxia to dilate the vessels. After injection the brains were hardened, embedded and cut. Serial sections were made from a block cut to take in the whole surface of the brain at the level indicated in Fig. 1. In these sections, micrometer measurements were made of the injected capillaries in the *Area Occipitalis* (area 17 of Winkler and Potter)<sup>10</sup> in the *area postcentralis* (area 1 to 3) and in the *area insularis* (area 13 to 16). Knowing the area covered by the square micrometer scale, and the thickness of the section, the length of injected capillary per cubic volume of brain substance could be fairly accurately measured for each hemisphere. Technical errors such as those due to shrinkage

in fixation become insignificant when only comparative measurements of the right and left hemispheres are used. As the left cervical sympathetic nerve was cut in each case, the left hemisphere

## AVERAGE OF 8 CATS

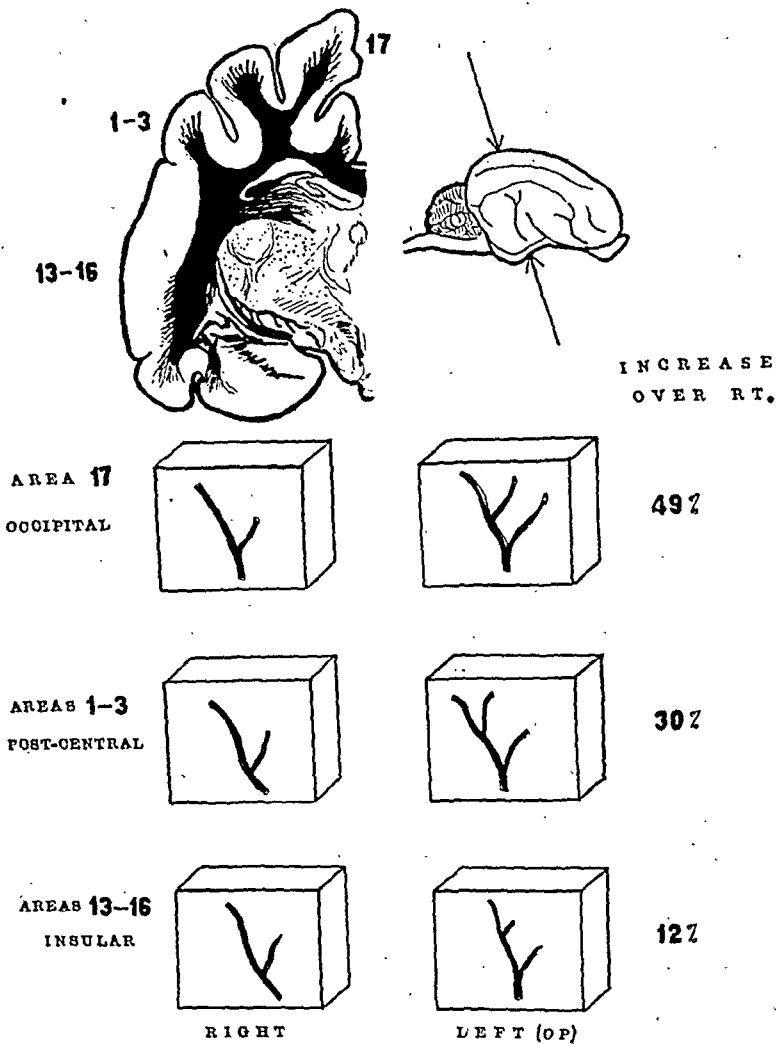


FIG. 1.—Diagram showing the increase in capillary bed in the left hemisphere after left cervical sympathectomy. Each block represents 100,000 cubic micra of cortical tissue, the bloodvessel drawn in represents the length of injected capillary measured in this block (about 62 micra in length, in the normal right hemisphere). After cutting the left cervical sympathetic nerve there is found by micrometry of the injected capillaries an increase of from 12 to 49 per cent in capillary bed in the left hemisphere. The arrows indicate the plane and level of section of the cat's brain. The sketch of the section at the left shows the location from which each of the three blocks of cortex were removed for microscopic examination.

is considered as the one experimented upon, and the right hemisphere is taken as the control.

Good preparations with even injections were obtained in 8 of the 10 animals. The capillary measurements showed that in every case more capillaries were open in the side operated upon (left hemi-

sphere) than in the normal right hemisphere. The greatest increase was in the *area occipitalis*, it was distinct but less marked in the *area postcentralis*, and very slight or negligible in the *area insularis*. According to Stöhr<sup>11</sup> there are several routes by which cerebral vasomotor nerves reach the brain; it is unlikely therefore that cutting the cervical sympathetic nerve on one side will completely denervate the ipsilateral hemisphere. This may account for the observed variations.

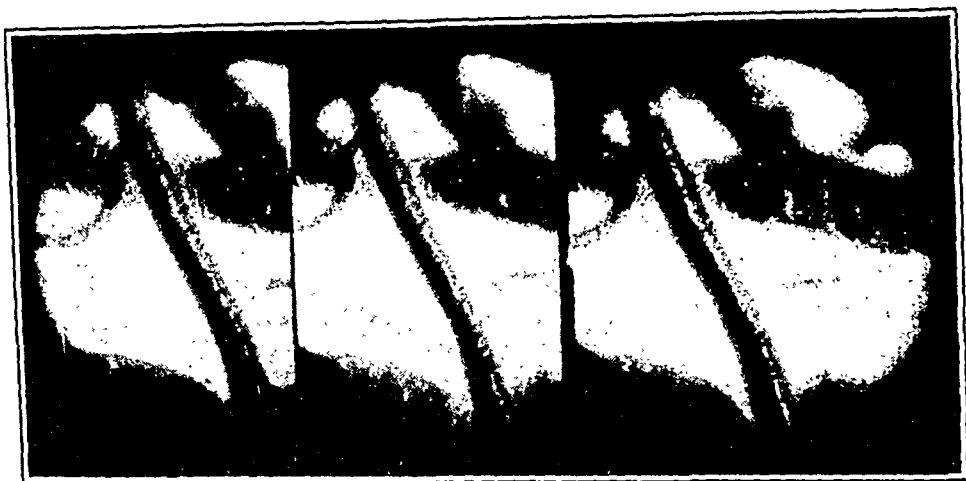
Taking all the observations and averaging them, a comparison of the side operated upon (left hemisphere) with the untreated side (right hemisphere) shows that in the *area occipitalis* there was an increase of 49 per cent in the length of injected capillary, in the *area postcentralis* an increase of 30 per cent, and in the *area insularis* an increase of only 12 per cent. The third figure is within the limits of probable error and means little. The other two are significant, especially because the two most important sources of error both tend to dilate capillaries and thus make less obvious the difference between the operated and normal sides. These sources of error are: (1) the unavoidable period of asphyxia at death; (2) the injection under a pressure of 220 mm. of mercury. Thus the conclusion seems justified that cutting the cervical sympathetic nerve causes an increase in the capillary bed of the ipsilateral cerebral hemisphere.

All the experiments so far described are indirect and therefore not entirely satisfactory, but there is a group of investigators who have directly observed the cerebral circulation through a trephine hole in the skull. Since the time of Brachet (1830)<sup>12</sup>, numerous authors have made microscopic observations of the living cerebral vessels and seen changes in the caliber of the vessels after stimulation, but their work was done with an open skull, a procedure which so greatly alters the intracranial pressure relationships that conclusions from their observations must be drawn with caution. Direct observation of changes in vessel caliber, however, can be regarded as crucial evidence, if the conditions of the experiment are essentially normal, and if the experiments are well controlled.

A window in the skull was first introduced by Ravina (1811).<sup>13</sup> Cushing (1901)<sup>14</sup> employed it to watch the effects of increased intracranial pressure. More recently Forbes (1928)<sup>15</sup> has greatly improved the technique by adding a washout system beneath the window, by applying micrometry and microphotography to the vessels observed, and by concomitantly recording arterial and cerebrospinal-fluid pressures. The observations made by Forbes and Wolff (1928)<sup>8, 16</sup> bring strong evidence to support the theory of vasomotor control. The pial vessels are seen to contract immediately after stimulation of the cervical sympathetic nerve and to dilate after stimulation of the central end of the cut vagus (see Fig. 2). During these reactions the systemic arterial pressure either remains constant, or rises during cerebral vasoconstriction and falls during cerebral vasodilatation.

Changes in the pressure of the cerebrospinal fluid in general parallel sudden changes in the diameter of the arteries, the pressure rising with dilatation and falling with constriction (see Fig. 3). These observations definitely controvert L. Hill's statement that the cerebral circulation passively follows changes in the systemic arterial pressure; they also add convincing data to the already considerable evidence of Weber, Hürthle and others.

In addition to experiments on nerve stimulation, much work has been done on the effect of adrenalin on the vessels of the brain. This, as a method for determining the presence of vasomotor nerves, is not entirely satisfactory, although such an authority as Gaskell (1916)<sup>17</sup> says that the action of adrenalin has proved the existence of vaso-



A

B

C

FIG. 2.—Photomicrographs of a pial artery taken through a window in the skull of a cat. *A*, two minutes before sympathetic stimulation. The artery is 58 microns in diameter. *B*, 40 seconds after a 60-second faradic stimulation of the left cervical sympathetic nerve (coil distance, 9 cm.). The artery shows a constriction amounting to 15 per cent of its initial diameter. *C*, at the end of a 60-second faradic stimulation of the left vagus nerve (coil distance, 9 cm.). The artery has dilated to 63 microns in diameter, which is 7 per cent larger than before the sympathetic stimulation. (See Forbes and Wolff.<sup>8</sup>)

constrictor nerves in the brain. Schilf (1926)<sup>18</sup> is of the opinion that the action of adrenalin in itself cannot be used as a proof of the presence of vasoconstrictor nerves. Such interesting work as that of Wiggers (1905),<sup>19</sup> who showed by perfusion of an excised brain that adrenalin decreased the outflow, should only be used as corroborative evidence of the existence of vasomotor nerves. The recent experiments of Gruber and Roberts (1926)<sup>20</sup> explain the former conflicting evidence in this field; apparently the dilatation of cerebral vessels following application of "adrenalin" recorded by several observers was due to the use of acid solutions, or to chloretone. Pure adrenalin alkaloid causes vasoconstriction if the solution is not acid.

Thus there is good evidence that the cerebral vessels contract on stimulation of the cervical sympathetic nerve, that they lose their tone and dilate when that nerve is cut, and that they dilate when the central end of the vagus nerve is stimulated. In other words, the

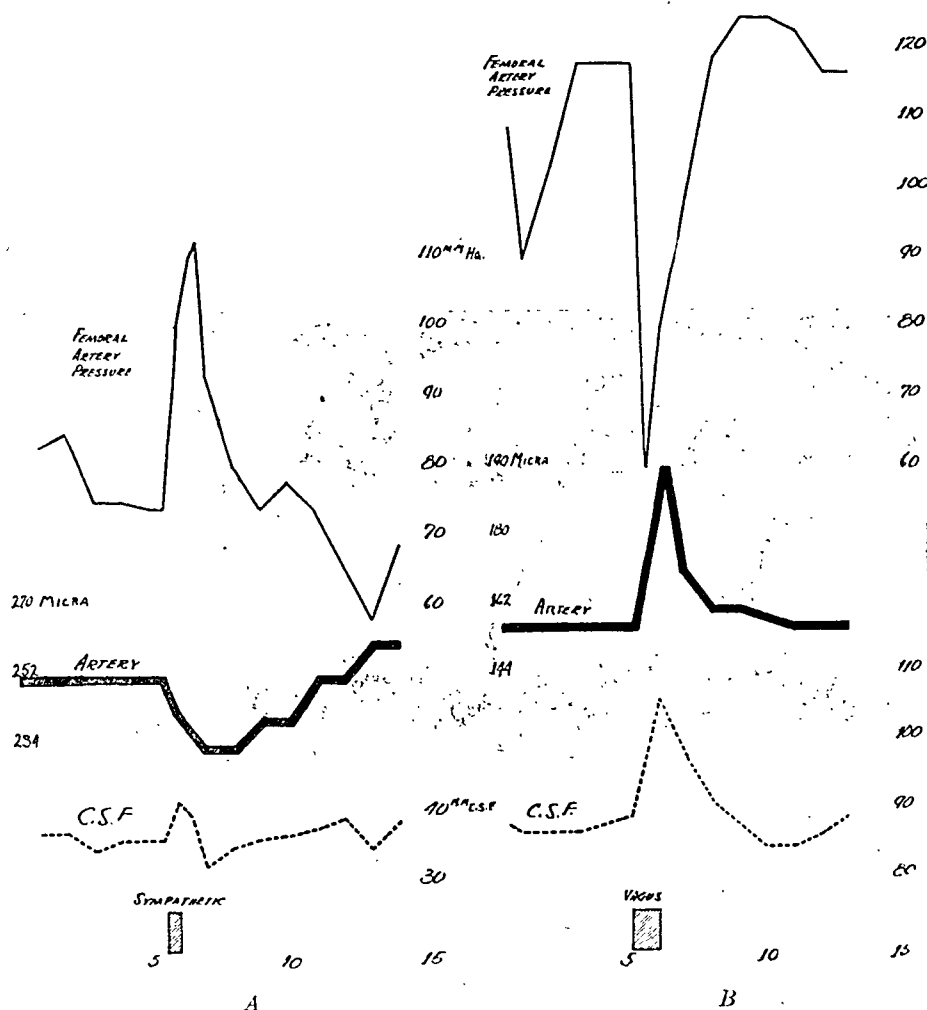


FIG. 3.—Two experiments by Forbes and Wolff showing the effects of (A) sympathetic and (B) vagal stimulation. Time is given on the abscissa in minutes. Faradic stimulation was applied to the nerves in the neck during the time covered by the shaded quadrangles. The lower dotted line gives the intracranial pressure measured in millimeters of cerebrospinal fluid registering in a manometer attached to a needle in the cisterna magna. The heavy middle line shows the changes in the diameter of the pial artery as measured under the microscope in micra. The upper line shows the variations in femoral artery pressure measured in millimeters of mercury. It is obvious that the changes in caliber of the pial artery are not only independent of, but in spite of, the changes in the systemic arterial pressure. (For other experiments and details see Forbes and Wolff, *Arch. Neurol. and Psychiat.*, 1928, 19, 1057-1086.)

bloodvessels of the brain react in the same way as vessels in other organs. It may well be that they react less strongly. Forbes and Wolff observed in the small pial arterioles an average reduction of diameter of only 8.5 per cent on sympathetic stimulation, and a

dilatation on vagal stimulation averaging 22 per cent of the diameter. From the functional standpoint, however, this is far from an insignificant change, for according to Poiseuille's Law (1842)<sup>24</sup> the minute-volume flow through a capillary tube of given length varies directly with the fourth power of the diameter of the tube. With a 22 per cent increase in diameter, therefore, there would be an almost 150 per cent increase in blood flow, that is the minute-volume would become two and a half times as great.

**Summary.** Taking all this evidence into consideration, it would seem that vasomotor control of at least the superficial cerebral vessels is now established. One must be guarded, however, in drawing clinical conclusions. Physiologically, it has been shown that pial vessels may constrict or dilate in response to appropriate stimulation, but in anesthetized animals the changes are not of great magnitude, and may be overcome by large variations in systemic pressures. L. Hill's statement, strictly speaking, still holds: "There is no evidence of a causation of cerebral anemia by spasm of the cerebral arteries." Real, obliterating angiospasm has only been experimentally observed when vessels are strongly and locally stimulated under nonphysiological conditions (Florey, 1925;<sup>21</sup> Wolff, 1927;<sup>22</sup> Lennox and Cobb, 1928.<sup>23</sup>) Recent investigations, however, certainly make vascular spasm a much more reasonable working hypothesis than it was thirty years ago.

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## LYMPHATIC ABSORPTION OF PARTICULATE MATTER THROUGH THE NORMAL AND THE PARALYZED DIAPHRAGM: AN EXPERIMENTAL STUDY.\*

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IN mammals, the diaphragm reaches its highest state of development and its functions are well defined and important. It contracts rhythmically and automatically with inspiration, increases the long diameter of the thorax, produces an increased intrapleural negative pressure and at the same time raises the intraabdominal positive pressure. It relaxes and the results are reversed. By this muscular action it has affected both the function of respiration and of circulation. Increase in negativity of pressure in the thorax brings air into the lungs and blood from the periphery through veins into the heart. Its voluntary contraction provides for an increase in intraabdominal pressure many times greater than that produced by its rhythmic action. This function not only permits extrusion of matter from the abdominal viscera, but at the same time prevents the increased pressure from embarrassing the action of the heart and lungs. It is a partition dividing the celom into two compartments, and as such it is a distinguishing characteristic of mammals. The partition, is

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pierced to permit continuity of vascular, alimentary and nervous structures. It is also permeable to permit the flow of fluids through channels, some of which normally are visible and others invisible: the lymph ducts and the lymph capillaries. To determine the nature of this flow from its source to its ultimate connection with the blood-circulatory system has been the purpose of this experimental study.

There was occasion for investigation because of clinical problems that long have remained unsolved. We wished to know: (1) why the base of the right lung suffers disease following abdominal operations, especially when the organs in the upper part of the abdomen are disturbed; (2) why infections of the peritoneum almost invariably cause an inflammatory response in the pleura, and (3) why pleural infection rarely involves the peritoneum. The solution, in whole or in part, of these problems depends on an investigation of lymphatic absorption. Fortunately, the diaphragm is an ideal structure on which to pursue such an investigation. It is a bilateral structure, each leaf of which is supplied by a single motor nerve. The factors of pressure and of muscular contractile movements, thought to be of significance in influencing the onset of postoperative phenomena, can be controlled at will by evulsion of one or of both phrenic nerves. The lymphatic drainage through a normal muscle may then be contrasted with that of a totally paralyzed one, and the relative speed of absorption and the quantity of absorbed material may be observed, as well as the vessels through which particulate matter flows. Only a proper medium is necessary. The medium must act as an indicator, and it must be particulate in character so that its absorption will simulate that of bacteria.

In the year previous to the start of this investigation, one of us (Higgins) with Graham<sup>1</sup> established five chief routes by which such particulate matter as we wished to employ might pass through the diaphragm. They found that "hydrokollag 300," a suspension of finely particulate graphite, was the most suitable medium, not only because it is black but also because it is a homogeneous mass of particles many times smaller than erythrocytes. By introducing this substance into the peritoneal cavity, they were able to allow the normal absorptive processes to fill the lymphatic vessels on the pleural surface of the diaphragm and the associated channels. This made visible the channels and made the direction of flow apparent. They believed that about 80 per cent of the material which passed through the diaphragm was carried by the lymphatic plexus of vessels which lies beneath the pleural surface of the diaphragm to the ventral surface of the sternum. From there it was transported to the large substernal lymph nodes which lie beneath the manubrium. The efferent vessels of these substernal nodes drain into the thoracic duct near its venous confluence, into the right lymphatic duct at the jugulo-



subclavian confluence, or indirectly through paratracheal mediastinal lymph nodes and thence to the thoracic duct. The system from the diaphragm to the substernal nodes was described as being plexiform, with loops of vessels passing from one side to the other. The plexiform nature of the vessels was especially noticeable after the vessels had passed the lymph nodes that lie in the spaces between the attachment of the first to the third ribs.

A second, or pulmonary, route that the material might take was found to be by way of a lymphatic vessel that passed backward over the vault of the diaphragm, thence upward parallel to the vagus to the nodes at the hilum of the lung. These in turn were connected by a plexus of vessels with the nodes in the arch of the aorta. Thence the course was to the paratracheal nodes which ultimately are joined, by small vessels, with the thoracic duct. In this course, there were tributaries that bridged across from side to side, making possible a final entry of the lymph either into both the right cervical or into the thoracic duct. They also described a small vessel passing upward, parallel to the phrenic nerve and vessels, into a paratracheal mediastinal lymph node on the ventral surface of the trachea, anterior to the arch of the aorta.

The third route described was by way of tributaries that passed over the vault of the diaphragm and thence cephalad on the posterior wall of the thorax to unite with the thoracic duct.

Finally, they described two groups of vessels that passed backward over the vault of the diaphragm and pierced it. One of these groups of vessels led to retroperitoneal lymph nodes in the neighborhood of the kidneys and the other to the large nodes in the splenic mesentery. All of these nodes were found to be directly connected, by lymphatic vessels, with the receptaculum chyli.

**Material and Methods.** In our study, we were desirous not only of repeating this work, but also of carrying the investigation further. We wished to determine the route and volume of drainage through paralyzed muscle and if possible to discover the mechanism that permitted particulate matter to pass through the muscular partition and into definite channels. The experiments were divided into 8 groups; dogs only were studied, and hydrokollag was the material injected in all but 2 cases. In these 2 cases, carmin and trypan blue were used.

Three dogs of the first group were anesthetized with ether and were operated on with the observance of careful surgical technique. The thorax was opened so that the movements of the diaphragm were visible. Then hydrokollag was injected into the peritoneal cavity and absorption into the subpleural lymphatics was observed. In other dogs of this group, a similar operation was performed; but previous to injecting the particulate matter, evulsion of the phrenic nerve was carried out, and the effect scrutinized. Later, hydrokollag was injected into the peritoneal cavity and its absorption into the

subpleural lymphatic vessels was observed both as to the time and degree of their filling.

The ten dogs of the second group underwent right phrenic neurectomy, at variable periods of time, from one day to eight months previous to the injection. All dogs were examined by fluoroscopic inspection before injection to be certain that the resulting paralysis was satisfactory and complete.

The three dogs of the third group were similarly operated on except that the phrenic neurectomy was done on the left side. The time previous to injection of hydrokollag into the peritoneal cavity varied in this group from one to three months.

The seven dogs in the fourth group underwent bilateral phrenic neurectomy from two to seven months before the absorption experiments were started. Otherwise, the technique was the same as in the other groups.

In the fifth group of six dogs, injection was made in the pleural cavity rather than in the peritoneal cavity.

In the sixth group, the pericardial space was injected.

In the seventh group of three dogs, operative work was not done, but the animals were fed melted butter in which hydrokollag, sudan III or trypan blue was intimately mixed.

In the eighth group of seven dogs, the injections were made directly into the cisterna chyli, into the descending lymphatic vessels lying on the posterior thoracic wall, or into the lymph vessels on the pleural surface of the diaphragm.

**Results of Injection into the Peritoneal Cavity.** The dogs were anesthetized and the ribs separated so that a view could be had of the movement of the diaphragm.

*Nerve Supply to Diaphragm Intact.*—In this group neither phrenic nerve was disturbed. It could be seen that the hemidiaphragm, under observation, moved normally with each inspiration. Hydrokollag was injected into the peritoneal space in amounts of from 30 to 40 cc., depending on the size of the dog. Within a period of three to four minutes, the lymphatic plexus on the dorsal surface of the diaphragm began to fill with the blackened material and the flow over the vault of the diaphragm was rapid and in the direction of the sternum. Most of the graphite passed forward into the substernal space and was lost to view. The filling of the lymphatics in the posterior portion of the diaphragm was less easily visualized and the direction of flow could not be easily determined. In other animals of this group, one phrenic nerve was severed before the material was injected into the peritoneal cavity. The immediate effect of division of either phrenic nerve was sudden paralysis and absence of movement of the leaf of the diaphragm on the side on which the nerve was severed. The muscle and the nerve were irritable and could be stimulated by mechanical measures. A marked contraction appeared on stimulation of the distal, cut end of

the nerve or when the muscle was directly irritated. However, when stimulation was not applied, the muscle was in a relaxed condition. When hydrokollag was introduced into the peritoneal cavity, it was seen that the period of time for filling the subpleural lymphatic plexus under observation was delayed. It usually could be seen filling the vessels ten to fifteen minutes after its introduction into the peritoneal cavity.

*Right Hemidiaphragmatic Paralysis.* In the second series of dogs, in which right phrenic neurectomy had been done at various periods preceding the neurectomy, examination with the fluoroscope was done as a routine to determine, before the intraperitoneal injection, whether or not perfect paralysis had occurred. In all instances, the right leaf of the diaphragm was high within the thorax and either had not shown evidence of movement with respiration or moved slightly in a paradoxical direction. The animals were injected forty minutes before they were killed by overetherization. At necropsy, the chest was opened by lateral incisions through the costosternal junctures, and the sternum itself was raised and carried downward, but it was not severed from the diaphragmatic attachments at the costal margins. Then both halves of the diaphragm could be seen. The appearance on the right side varied from normal to one of advanced atrophy, depending on the length of time that had elapsed between phrenic neurectomy and the intraperitoneal injection. Up to a period of approximately two weeks, there was no visible evidence, either in its thickness, color or opacity, that the muscle was paralyzed. However, it retained marked irritability, so that stimulation of the muscle itself, or of the distal end of the cut nerve, caused more vigorous contraction than was found when the same interference was used on the normal side. The degree of irritability, however, decreased with the passage of each day until a period of two weeks had passed; then the irritability was markedly lessened or lost, and the muscle became more flaccid, attenuated and less opaque than normal. In the groups in which neurectomy had been done eight months previous to the injection, the muscular tissue was so atonic that it had become transparent and the muscular fibers had lost their color to such an extent that it was only with great difficulty that one could distinguish the division between the central tendon and the muscular portion. The atrophy in every instance was limited to exactly one leaf of the diaphragm; the whole hemidiaphragm, from center to periphery, was paralyzed and there was neither evidence of nerves crossing from the uninjured to the paralyzed side nor of regeneration of nerves on the paralyzed side.

In normal animals, the lymphatic plexus on the right side is much more pronounced than it is on the left. This likewise is true, even though the muscle on the right is paralyzed and that on the left normal, and the direction of the lymphatic current in these animals is the same as that in normal dogs. All the five principal paths

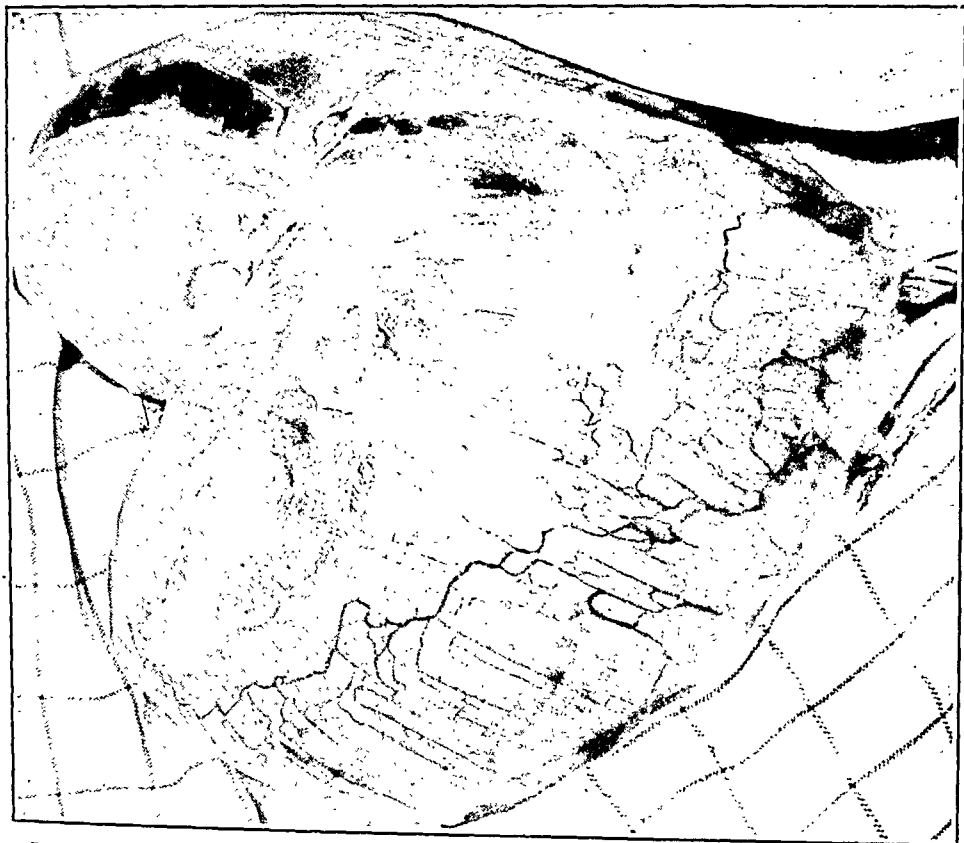


FIG. 1.—Lymphatic drainage on the pleural surface of the right hemidiaphragm, forty-five minutes after peritoneal injection in a dog on which right phrenicotomy had been performed four days before.



FIG. 2.—Section of the diaphragm, ten minutes after peritoneal injection of graphite in a normal dog. Graphite may be noted in subserous lymph vessels (corrosive fixative,  $\times 100$ ).

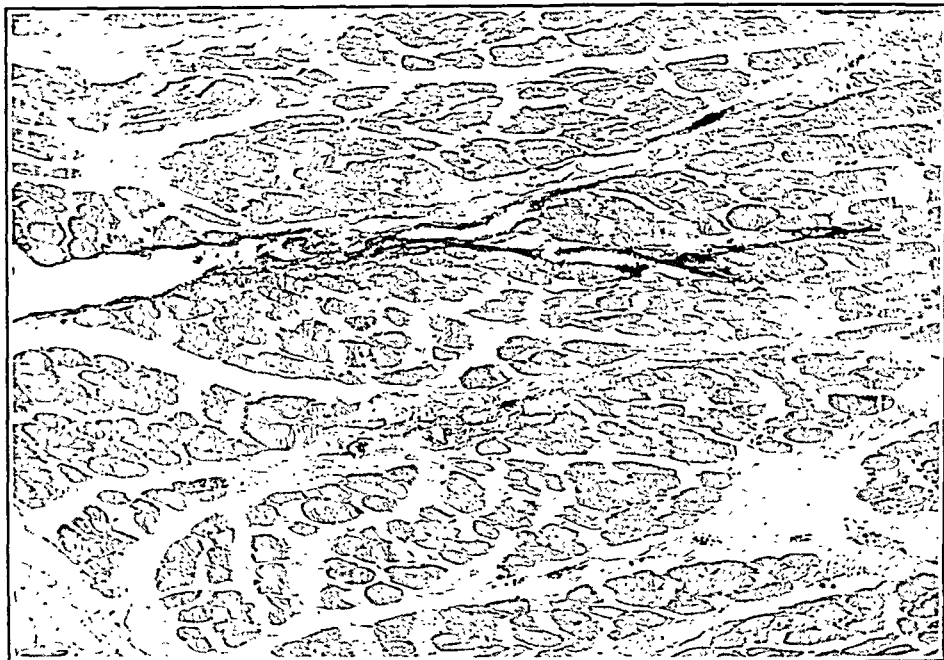


FIG. 3.—Section of the diaphragm, ten minutes after peritoneal injection of graphite in a normal dog. Graphite may be noted in channels coursing through the diaphragm (corrosive acetic fixation,  $\times 100$ ).

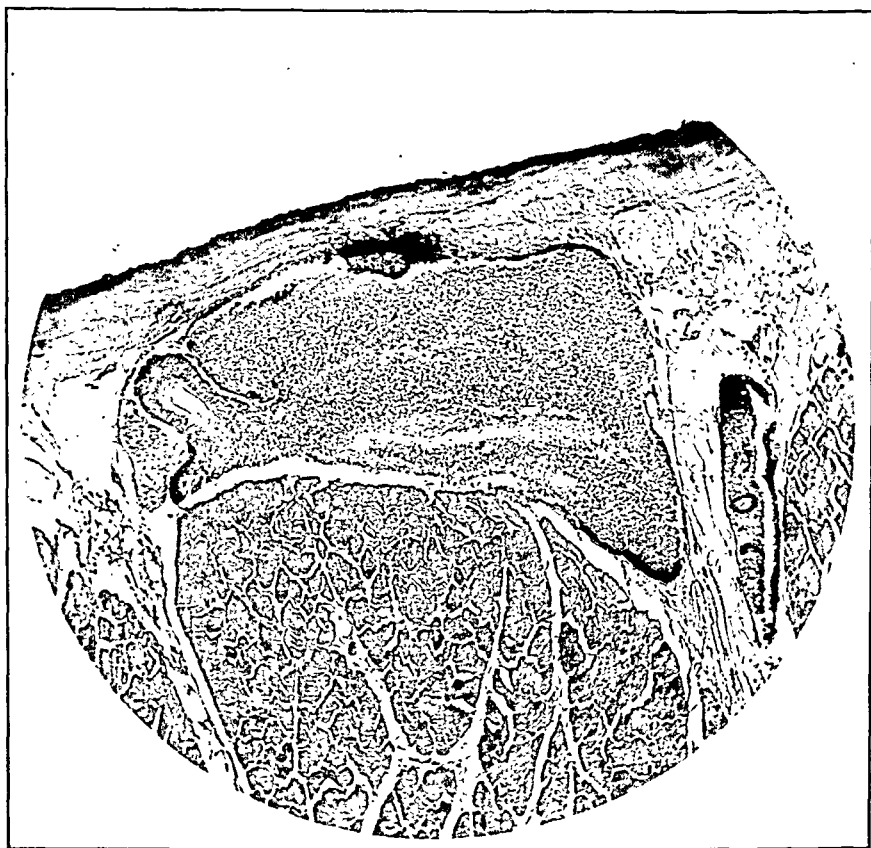


FIG. 4.—Section of the diaphragm, ten minutes after peritoneal injection of graphite in a normal dog. Large subpleural collecting lymph channel is filled with graphite (corrosive acetic fixation,  $\times 100$ ).



FIG. 5.—Section of the diaphragm, ten minutes after peritoneal injection of graphite in a normal dog. Graphite granules may be seen passing through serosal surface to enter subserous channels (corrosive acetic fixation,  $\times 100$ ).

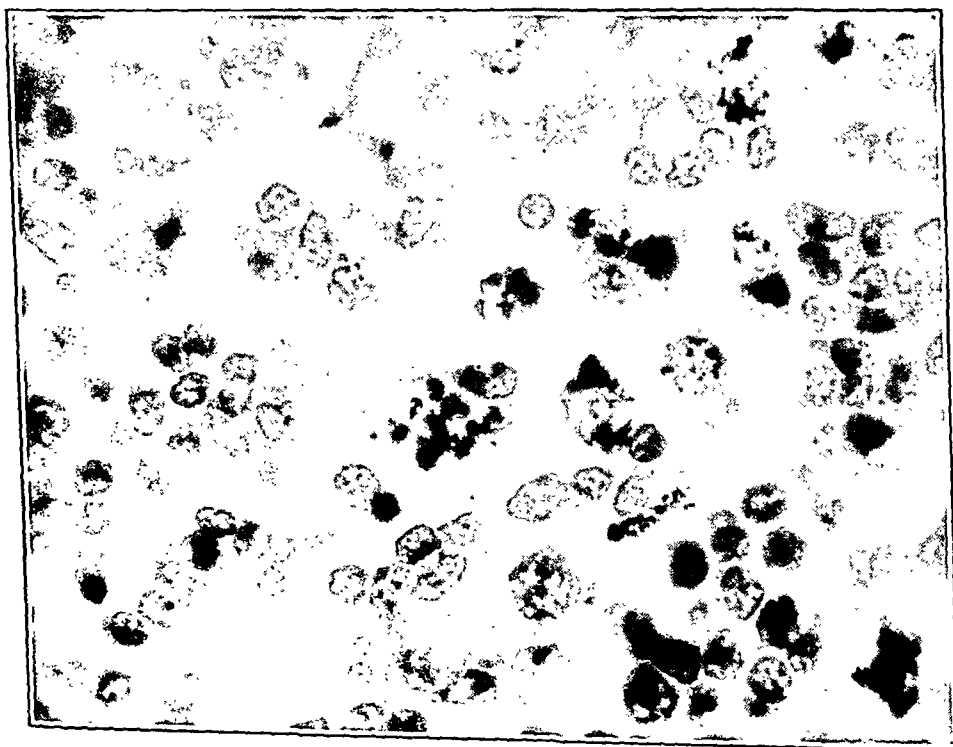


FIG. 6.—Section of large lymph node, adjacent to spleen in a dog forty-five minutes after the peritoneal injection of graphite. Large macrophages in gland containing graphite from lymph channels draining diaphragm may be noted ( $\times 1000$ ).



can be demonstrated. Much the larger portion of the graphite passed forward over the vault of the diaphragm, upward through the plexus of lymphatics in the neighborhood of the internal mammary vessels and passed thence to the group of substernal lymph nodes from which small channels provided drainage into the thoracic duct. In the neighborhood of the substernal lymph nodes, the anastomosing vessels passed from one side to the other so that the lymph and particulate matter poured not only into the thoracic duct but a portion of it went also to the right cervical duct. In some cases, a descending lymphatic vessel could be found lying on the posterior wall of the thorax, and passing downward it penetrated the diaphragm and led into the lymph nodes that lie in the region of the kidney. This direct retroperitoneal drainage, however, occurred not only by this single vessel, but also by vessels passing over and downward across the vault of the diaphragm posteriorly. Either independently or after confluence with the descending vessel, these channels entered the same nodes in the region of the kidneys. The nodes themselves in turn were connected with the cisterna chyli by a variable number of small vessels. Also, there were instances in which small channels on the posterior surface of the diaphragm could be traced directly into the thoracic duct. They passed downward and entered the duct as it presented itself through the dorsal surface of the diaphragm. In other instances, the vessels after leaving the vault of the diaphragm passed upward on the posterior wall of the thorax before they entered the thoracic duct. Similarly, particularly on the left side, lymphatic vessels could be found which passed backward to a point anterior to the aortic opening in the diaphragm, and there, piercing the diaphragm, they entered the abdominal cavity and drained into a large lymph node or group of nodes lying in the splenic mesentery in the neighborhood of the pancreas. These nodes were directly connected, by a group of small vessels, with the cisterna chyli.

*Left Hemidiaphragmatic Paralysis.* When the left hemidiaphragm had been paralyzed for various periods of time preceding the intraperitoneal injection of hydrokollag, similar observations could be made, excepting that in no case was the drainage through the left side equal to that through the right side. The vessels themselves were smaller in size and fewer in number and apparently carried much smaller streams of particulate matter through them. In some instances, the amount was so small that the subpleural lymphatics were but faintly outlined. In others, the pattern could be very definitely made out, and all the main tracts that have been described could be readily shown.

Other channels were sometimes observed, although they were not always seen. The chief one of these subordinate channels was small and carried the particulate matter over the surface of the esophagus, parallel to the vagus, and upward to the lymph nodes



at the hilum of the lung. These were densely blackened and communicated by irregular channels with the lymph nodes at the arch of the aorta and the peritracheal nodes. From these nodes vessels deposited the hydrokollag in the lymphatic and thoracic ducts at their jugular confluences. On the left side, in one or two instances, very small vessels could be seen coursing over the diaphragm, passing upward along the phrenic nerve and vessels, and carrying its stream of particulate matter to a paratracheal lymph node. This vessel was never seen on the paralyzed side, probably because during evulsion of the phrenic nerve it had become obstructed.

*Bilateral Diaphragmatic Paralysis.* In the series of seven dogs on which bilateral phrenic neurectomy was done, the absorption through the diaphragm was delayed and the amount of material passing through the vessels seemed to be much less than in normal animals or in those with hemidiaphragmatic paralysis. There seemed to be no doubt that the contraction of the diaphragm itself had an influence in increasing the flow of lymph. Massage of the abdomen, pressure exerted on the abdomen, or muscular activity in the period of time elapsing between the injection of the particulate matter and necropsy did much to increase the drainage and to fill the plexus of subpleural lymphatics. All of the lymphatic tracts, however, were exactly the same as those in normal animals. The only variability from normal was in the speed of flow and amount of material carried.

In three animals that had undergone bilateral phrenic neurectomy three weeks before injection, 40 cc. of hydrokollag was injected into the peritoneal space and allowed to remain there for variable periods of time. Observations at necropsy were made ten, sixteen and twenty-four days, respectively, after the injection. When the abdomen was opened, it was found that the peritoneum was dry, but that the omentum was deeply stained with graphite which seemed to be caught in its meshes and fixed there. When the neck was opened, the thoracic duct was shown to contain only clear lymph, and its juncture with the vein could readily be demonstrated. Material taken from the thoracic duct failed to show any evidence of graphite. After the chest was opened, along the two sides of the sternum, the anterior mediastinum was seen to contain some blackened areas which indicated that hydrokollag had found its way into the lymphatics. The lymph vessels on the dorsal surface of the diaphragm, however, could be but indistinctly seen and did not contain graphite. The diaphragm itself had the same appearance, both on the ventral and on the dorsal surface, and it was blackened in patches which represented an accumulation of the pigment between the muscle bundles. The muscle in all three of these cases was thoroughly paralyzed and translucent. The substernal muscles were deeply and diffusely injected with the graphite, but showed an accumulation of material running in indistinct lines toward

the lymphatic vessels that lay beneath them and passed upward into the group of substernal lymph nodes. These were markedly enlarged and densely blackened. All the lymph nodes in the neighborhood of the trachea, in the region of the aortic arch and about the hilum of the lung were heavily infiltrated with graphite. The two lymph nodes in the region of the kidney and the one in the region of the spleen were also densely infiltrated and markedly enlarged; some of them measured 3.75 by 0.5 cm. These observations suggested that the lymphatics had drained all of the particulate matter possible into the lymph nodes and thence to the venous confluences of the lymphatic ducts. However, when these were overfilled further absorption failed to take place and the intervening lymphatic chains were emptied and could not be traced at necropsy. In the dog that had been injected sixteen days previous to necropsy, the diaphragm was more densely filled with hydrokollag than in the earlier experiment and the intercostal muscles lying between the seventh and eighth costal margins were deeply infiltrated. The infiltration pointed upward toward the median line and seemed to show a connection between the intercostal muscles themselves and the substernal muscles. There also was slight infiltration with hydrokollag in the anterior mediastinum in this animal. Infiltration could be made out in the pericardial attachment to the diaphragm and in the ligament of the left lung. The lung and visceral pleura were free from infiltration of any kind and the pericardium did not give evidence that it had absorbed particulate material. After removal of the diaphragm, it was seen that there were blackened areas throughout its fibrous portion and very fine vessels at the juncture of the fibrous with the muscular portion joined with the lymphatics in that region. In the early experiments, we were unable to find any similar evidence of absorption through the fibrous areas of the diaphragm.

*Systemic Fate of the Particulate Matter in all Experiments with Intraperitoneal Injection.* In all instances of peritoneal injection, regardless of the operation done on the phrenic nerve, the peritoneal surface of the diaphragm bore a smoky appearance. The graphite was distributed uniformly over the surface and attached to it. The fluid removed from the abdominal cavity proved that some of the graphite was free and that some was included within phagocytic cells. Some particles of graphite from the lymphatic plexus on the pleural surface of the diaphragm were found to be floating freely in lymph and some were included in phagocytic cells. The phagocytic cells were few in number. When the thoracic duct was blackened and was pouring its contents into the venous stream, it contained both free particles of graphite and particles enclosed in phagocytic cells, but the proportion enclosed in cells was much larger than that in the lymphatic vessels of the diaphragm. The blood stream itself contained free graphite but it also contained cells packed with

particles which showed that phagocytosis had occurred. In some instances, the blackened lymph stream in the thoracic duct could be observed as it flowed into the veins within thirty to ninety minutes after the peritoneal injection. The tissue juice pressed from a cut surface of any of the lymph nodes contained graphite both in the free state and also enclosed in phagocytic cells. The greater amount was intracellular.

**Results of Injection into the Pleural Space and the Pericardium.** Injections that were made into the pleural cavity were done to determine whether or not absorption would take place through the pleural surface of the diaphragm. There was not an instance in which the visceral pleura of the lungs or the pleural surface of the diaphragm showed any evidence whatever of absorption. The lymph nodes in the region of the kidneys, however, were blackened, probably because of the presence of the descending vessel that lies on the dorsal aspect of the thorax. The absorption was not through the diaphragm itself. The subpleural lymphatic plexuses were always free of the medium and hydrokollag was not present between the muscle bundles or on the peritoneal surface of the diaphragm. This particular type of experiment, in which the pleural cavity was injected, is incomplete and will be the subject of further investigation. It was done at this time simply to determine whether or not absorption occurred through the pleural as well as through the peritoneal surface of the diaphragm. The same is true of experiments in which injections were made into the pericardium.

**Results of Feeding Dyed Food.** In the feeding experiments, the only significant observation that could be made was that absorption did not occur through the diaphragm itself. All of the absorption appeared within the thoracic duct. When the food was stained with sudan III, all of the lymphatics of the abdomen were stained pink, the cisterna chyli itself was filled with pink lymph, and the thoracic duct poured its colored lymph into the blood stream.

**Results with Injection into the Lymphatic Apparatus.** In all of the experiments that have been described previously, the course of the lymphatic stream was determined by the natural absorption mechanism of the body. In the final group of experiments, the normal courses that had been observed were made more clear by injection into the lymphatic channels. These were of two types: injections into the cisterna chyli and injections into descending lymphatic vessels of the thorax.

Injections of the particulate matter directly into the cisterna chyli outlined the passage of the lymph through the thoracic duct and thence into the blood stream. In some instances, the tributaries were filled and the connection between the thoracic duct and the posterior intercostal lymph nodes could be discovered. In other instances, vessels not commonly seen passed directly from the thoracic duct to the nodes at the hilum of the lung. The connecting

lymph channels between the hilar nodes and the chain of lymph nodes along the trachea could be filled, and the course could be followed to the juncture with the duct at its confluence with the veins. When the descending lymphatic vessels in the posterior wall of the thorax were injected, the lymphatic tract could be followed easily as it pierced the posterior attachment of the diaphragm and passed downward to the lymph nodes in the neighborhood of the kidneys.

The same result could be obtained if the appropriate trunks that passed downward over the vault of the diaphragm were injected. Their connection with the retroperitoneal lymph nodes could easily be demonstrated. Likewise the lymphatic vessels passing backward to the anterior surface of the aorta could be injected and followed directly to the lymph nodes lying in the splenic mesentery. When the several groups of lymph nodes were injected the tiny vessels connecting them with the cisterna chyli could be traced (Figs. 1 to 6).

**Comment.** We have found it difficult to correlate experimental data with clinical observations of disease in the lower lobe of the right lung on the basis of the lymphatic drainage. This is particularly true because we were unable to discover at any time lymphatic tracts within the lung through which the current coursed toward the periphery. There was no difficulty in discovering the course of lymph from the peritoneum to the hilar lymph nodes, but the course beyond, within the lung, was not evident. This is probably because the lymphatics within the lung flow toward the hilum. To ascribe infection to a lymphatic route would force one to admit that the infection spread into the lung against the normal current. Experimentally, we have been unable to force lymph through channels in the direction opposite to the normal flow. The lymphatic vessel itself ruptures before the valves give way. However, the problem of infection within the lung is more or less an academic one as far as the source of infection is concerned. We were able to discover that particulate matter passed through the diaphragm within a period of three to five minutes, but it also was found in the blood stream within thirty to ninety minutes. The period between the peritoneal injection and the finding of particulate material in the blood current is too short to permit one to distinguish, from a clinical standpoint, between lymphatic and blood-borne infections.

The circumstances regarding the inflammatory response in the pleura are somewhat more easily understood. The plexus of lymphatic vessels fills very rapidly, and the lymph, carrying particulate material, is separated from the pleura only by the pleural mesothelium. Therefore, by mere continuity of tissue, the infection might readily set up inflammatory reaction of the pleura, and cause an effusion to appear within the pleural cavity. This would be more likely to occur on the right side because of the much larger lymphatic

drainage—through the right portion of the diaphragm. It is significant that the lymphatics of the right leaf of the diaphragm carry a greater amount of material than those of the left, even when the muscle of the left side is normal and that of the right side is paralyzed. It is also significant, however, that the flow does not appear until a later period when the muscle of the diaphragm is functionless.

Another problem that seemed to us of significance before we started the work had to do with the rarity with which pleural infection involves the peritoneum. The solution is not at all evident from our experimental work. We are hoping that when the work on pleural injections is completed, something more may be said regarding the problem. The only facts we have at present are two: first, the pleural covering of the diaphragm does not absorb material injected into the pleural space; second, the descending lymphatic vessels carry particulate material from the thorax into the retroperitoneal space and the lymphatic vessels of the diaphragm carry it into the lymph nodes that lie in the splenic mesentery. It would seem possible that chronic infections, such as empyema, may obstruct the flow of lymph in which bacteria are being carried by sealing these tracts so that infection does not proceed into the peritoneum or the retroperitoneal region.

**Summary and Conclusions.** 1. These experiments on absorption through the normal and the paralyzed diaphragm confirm the observations made by Higgins and Graham that five main channels carry the particulate matter from the peritoneum upward through the thorax and into the blood stream.

2. These five routes and their functions are as follows: the first, the sternal route, which is much the most important, is that by which at least 80 per cent of the particulate material is carried. The second, the pulmonary route, is represented by a small vessel that empties its lymph into the nodes at the hilum of the lung and by a vessel that is parallel to the phrenic artery and nerve and carries its lymph to a node in the anterior mediastinum. The third route is through the thoracic duct which receives as tributaries small vessels that pass over the dorsal portion of the diaphragm and enter it in various positions along its course. The two remaining routes, the fourth and fifth, are represented first by vessels that pass over the dorsal surface of the diaphragm, pierce it, and empty their lymph into the lymph nodes in the region of the kidney, and second, by small vessels which also pass over the vault of the diaphragm to a point anterior to the aortic opening where they pierce the diaphragm and pass downward into the splenic mesentery and pour their contents into the lymphatic node in the region of the pancreas. All of the nodes which receive the tributaries are in turn connected by vessels with the receptaculum chyli.

3. The experiments also have demonstrated the presence of a descending thoracic vessel which passes downward over the posterior

wall of the thorax, sometimes receiving tributaries from the vessels of the posterior portion of the diaphragm and communicating with the lymph nodes in the region of the kidney.

4. The particulate matter seems to be taken up diffusely on the under surface of the diaphragm. It passes between the mesothelial cells of the peritoneum into tiny lymphatic vessels and thence is carried between the muscle bundles until it is deposited within the subpleural plexus of lymphatic vessels. This transfer from the peritoneal surface to the pleural surface is rapid; it requires only from three to five minutes in normal muscle and from ten to twelve minutes in paralyzed muscle.

5. The penetration of particulate matter into the blood stream is effected within a period of from thirty minutes to one and a half hours.

6. The lymph taken from the lymphatic vessels on the surface of the diaphragm is mainly found in a free state, although a few phagocytic cells also contain some of it. The material taken from lymph nodes is found mainly to be enclosed in phagocytic cells, although a slight amount is still free. That which comes later through the thoracic duct is mostly enclosed within the phagocytic cells, but some particles are still in a free state. When obtained from the blood, it is both in free state and enclosed in phagocytic cells. It is probable that the monocytes take up the free material very quickly after it has been passed into the blood stream.

7. There is no question but that normal muscular contraction of the diaphragm contributes much to the passage of the particulate matter through the diaphragm. Nevertheless, the difference in size of the lymphatics on the two leaves of the diaphragm also is important. The lymphatics on the right side are much larger and carry a much larger proportion of the lymphatic flow than those on the left. Even after paralysis of the right half of the diaphragm, the pattern discovered after the lapse of thirty minutes is more distinct on the paralyzed right side than on the normal left side. Absorption through the left half of the diaphragm, when that half is paralyzed, is insignificant. Often the vessels are but indistinctly outlined.

8. It is apparent from the evidence obtained in the prolonged absorption experiments that the primary flow of particulate matter stops as soon as the lymph nodes become choked with graphite.

9. It is our belief that the lymphatics of the diaphragm are concerned with absorption from the peritoneal space.

#### REFERENCE.

- <sup>1</sup> Higgins, G. M. and Graham, A. S.: The Lymphatic Drainage from the Peritoneal Cavity in the Dog, Arch. Surg. (in press).

## THYRONEURAL DYSTROPHY.

## THE ASSOCIATION OF CONGENITAL MYXEDEMA WITH MENTAL AND NEUROMUSCULAR DISORDERS.\*

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THE well-known association of mental defect and thyroid insufficiency indicates the close interdependency during growth of the central nervous system and the thyroid gland. Cases of thyroid deficiency (cretinism, congenital myxedema) associated with neural defects other than mental have been rare. Well-known textbooks do not mention them. It will be shown in the following that thyroid deficiency may be associated with such brain defect as will lead to mental defect, and with disease of phylogenetically older neural structures. As a result, serious disorders of neuromuscular control, manifested in various grades of diplegia, ataxia, chorea, and so forth may coexist with thyroid insufficiency.

**Historical Survey.** The first note of the condition which we have found is in 1908, when McCarrison<sup>1</sup> first drew attention to "the frequent association of a definite train of nervous symptoms associated with cretinism. These symptoms were present in 71 cases among a total of 203 cretins, and appeared to me to constitute a definite type of disease to which I applied the term 'nervous cretinism.'" These cases were observed in British India, in the Chitral and Gilgit Valley. McCarrison pointed out that various degrees of cerebral diplegia were associated with the cretinism, and either the thyroid or cerebral manifestations might predominate almost to the exclusion of the other.

McCarrison further stated that "the signs of derangement of the central nervous system may vary from the slightest degrees of paraplegia to the most intense grades of spasticity, athetosis, fits and

\* The diagnosis of these cases as belonging to the same group as those reported by McCarrison was made at Montefiore Hospital in 1922 by S. A. K. Wilson, M.D., of London, and some of the literature herein quoted was sent by him to one of us (W. M. K.) shortly thereafter. For this help we wish to express our thanks.

idiocy. Nystagmus, which is rare in the purely myxedematous forms, may be present in these cases, and squint is common."

In 1913, Crookshank,<sup>2</sup> in reporting a case of cretinism showing "ataxic paraplegia," observed that there are three varieties of nervous symptoms: (a) choreiform; (b) ataxic, (c) spastic. In the same year, Langmead<sup>3</sup> also reported a case.

In 1910, Manson<sup>4</sup> reported 2 cases of cretinism in twins, one of whom had epileptiform seizures and one cerebellar symptoms. Söderbergh's case,<sup>5</sup> published the same year, showed bilateral adiadochokinesis and cerebellar catalepsy of Babinski. These signs disappeared after thyroid medication. In 1914, Vetlesen<sup>6</sup> presented 3 cases in which myxedema and paralysis agitans were associated. In 1923, Barkman<sup>7</sup> published a case with symptoms of cerebellar and extrapyramidal disease. He believed that in myxedema there is a toxic effect upon the cerebellum and basal ganglions. The neural signs and symptoms disappeared under thyroid administration. In De Quervain's experience<sup>8</sup> the neural signs often ran parallel to the intensity of the symptoms of cretinism. Lundberg<sup>9,10</sup> described 7 cases with cerebellar signs. Eaves and Croll<sup>11</sup> reported a case of myxedema with convulsions. In most of these cases, beneficial results followed the administration of thyroid. On the other hand, after studying a series of 1700 feeble-minded children, Naville<sup>12</sup> believed that disturbances of the thyroid play no great part in the etiology of congenital diplegias. In 1922, Barlow<sup>13</sup> examined vestibular irritability in 15 cases of myxedema, and found that there was reduction of irritability of the eighth nerve. One large group of possibly related cases has been found, notably that reported by Chagas<sup>14</sup> in 1913. The majority of these cases, which Chagas attributed to the *Trypanosoma cruzi*, began in infancy ("premières années de leur existence").

Briefly, therefore, we are confronted with a disorder of the thyroid gland of congenital origin, associated not only with mental defect, but also with motility disorders of various kinds and severities. Before discussing the various aspects of this curious combination of endocrine and neural defect, we shall present 2 cases occurring in one family.

**Two Case Histories.** (R. and N.) *Family History.* The cases are a girl and a boy in a family of seven children, all the others of which are normal. The ages at present are twenty-nine, twenty-eight, twenty-six, twenty-four, twenty-one, nineteen and sixteen years. The oldest, R., a girl, is most severely affected; the next to youngest, N., a boy, but slightly. Indeed, if any comparison were made, it would be that R. shows less thyroid defect and more nervous defect, while N. shows the reverse. There is no thyroid or neural defect in the parents or in the history of the family. The mother and father are first cousins. The father is flat-footed, a fact which is of especial interest in connection with the foot deformities of R. and N.

**CASE I.—Development.** R., aged twenty-nine years. She has been ill since birth. Icterus neonatorum persisted for the first six months. She



walked for the first time at three years, talked at five years. The anterior fontanelle closed at seven years. Cretinism was diagnosed early, and R. has been given thyroid on and off for at least twenty years. She had scarlet fever, diphtheria, measles and frequent attacks of sore throat during childhood, but as far as can be discovered, these illnesses had no effect upon her condition. At the age of eight, R. went to school, but having remained in the same class for three years, she was put in ungraded classes, where she remained until the age of fifteen. She learned to read and write and do simple arithmetic. R. then went to work. She began to typewrite, became a typist, and continued at this occupation until the age of nineteen. She then worked in a factory, boxing neck-ties, until the age of twenty-one, when she stopped work. She has not done any since. At the age of twenty-four, she still showed unmistakable signs of mental defect. The menses began at seventeen years, but have been extremely irregular, often appearing only at two- and three-month intervals. Dyspnea on exertion and excessive perspiration at night have also been complained of for some time.



FIG. 1.—Facies in thyreoneural dystrophy (Case R). Note enlarged thyroid gland.

*History of Neural Defects.* At the age of eight, R. began to stutter. This remained about the same until 1920 (age twenty-one years) when it gradually became much worse. At that time there were also deformities of the feet and a peculiar unsteady gait. About 1922, spasmodic flexor movements of the right upper and later both lower extremities appeared.

R. states that at about the same time, she became subject to "fainting attacks" and that she would fall to the ground. There were no convulsions. She describes these attacks as first dizziness, then a feeling of twitching of the eyes, then a feeling of cold and then falling. "Afterward I do not know what happened to me." There is no tongue-biting, convulsion, incontinence or aura. She does get pale before fainting. While the patient was in Mount Sinai Hospital in 1921, these static seizures were observed by a nurse who found her lying in a heap on the floor. She was also found unconscious on the floor by her employers on several occasions. Frontal headaches and spells of dizziness are also complained of.

R. states that occasionally she has attacks of laughter without provocation. Cold hands and dry skin are stressed, together with frequent "choking" when eating solids or liquids.

R. has complained of very persistent constipation; this has been confirmed by observations made at Montefiore Hospital. All efforts to induce normal bowel movements have been unavailing. She states that she has attacks of vomiting, but these have never been observed in the hospital. Sharp epigastric pains occur, worse after meals and associated with some nausea. She has noted frequency of urination—eight to ten times a day, and twice at night.

**Examination.** 1. *General.* She is an overnourished, well-developed young woman, who looks her age, twenty-nine years. The skin is dry and of a yellowish hue; the lips exhibit good color at times, at others show definite pallor. The hair is dry. It is abundant upon the head. The axillary and pubic hair is normal. The throat and fauces are normal. Heart, lungs and abdomen are negative. The blood pressure is 100 systolic and 70 diastolic. There is no bony disorder and no spinal curvature. The thyroid is definitely enlarged and soft to the touch (Fig. 1).

The urine is normal, the blood Wassermann negative. The basal metabolism (1921) is  $-15$ . The hemoglobin is 95 per cent. Blood chemistry follows: Urea nitrogen, 18.2; incoagulable nitrogen, 42; uric acid, 3.9; creatinin, 2.2; cholesterin, 0.13; blood sugar, 0.090 per cent.



FIG. 2.—Dorsi-extension of the left big toe (Babinski sign) in Case R.

Roentgen ray report, December 17, 1920: "Stereoradiographic examination of the skull shows the sella turcica to be somewhat irregular, with atrophic posterior clinoid processes, apparently bridging over the entrance to the sella. The sphenoidal sinus appears very small. The bones of the skull are thick and do not show any signs of intracranial pressure, but there is a small area on the vertex of the skull which is rather suggestive of an atrophic process in the left parietal bone (fontanelle?)." "Examination of the hands shows a normal condition for her age."

2. *Neural.* *Cranial nerves:* Negative. *Sensation:* Normal for deep and cutaneous types. There is no Romberg or ataxia in the trunk or extremities. *Reflexes:* Normal except for the reaction of the great toe. It is almost constantly in extension on the left. When plantar stimulation is tried (Fig. 2) extension results on both right and left sides. *Motility:* There is no atrophy of muscles. Possibly R. is not as strong as her heavy build would lead one to expect. She stutters very markedly, and when speaking there are spasmodic, associated movements of the face and right upper extremity. The latter is involuntarily flexed. At times the same type of movement is noted in the left face and the left upper extremity in lesser degrees. Again, there are flexor movements of trunk and hips. While seated, the left leg is drawn up when speaking. In 1920, this was the only abnormality. In 1923 (age twenty-four years), she often had movements of the left extremities, and occasionally of the right lower when speaking.

This made her sway almost continually when she conversed. The movements also occur when she is not speaking. They recall athetosis on the one hand, chorea on the other. One is also reminded of certain cases of dystonia musculorum deformans.

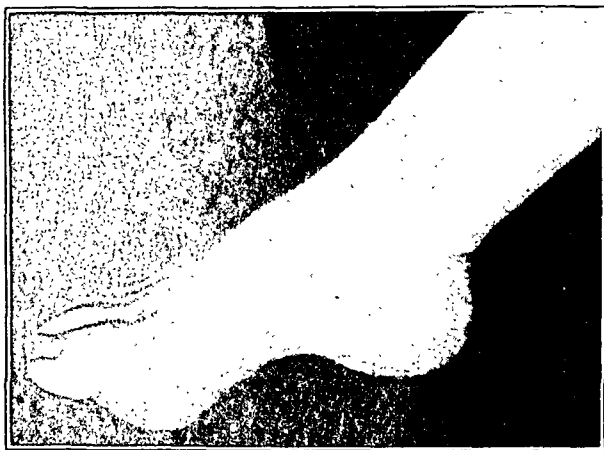


FIG. 3.—Pes cavus in Case R (thyreoneural dystrophy).

The feet are both deformed and show the typical pes cavus seen in Friedreich's ataxia (Fig. 3). But there are no other signs of this condition, beyond the dorsiflexion of the great toes. The cavus is marked, the extension of the great toe at the proximal joint and flexion at the distal is well seen.

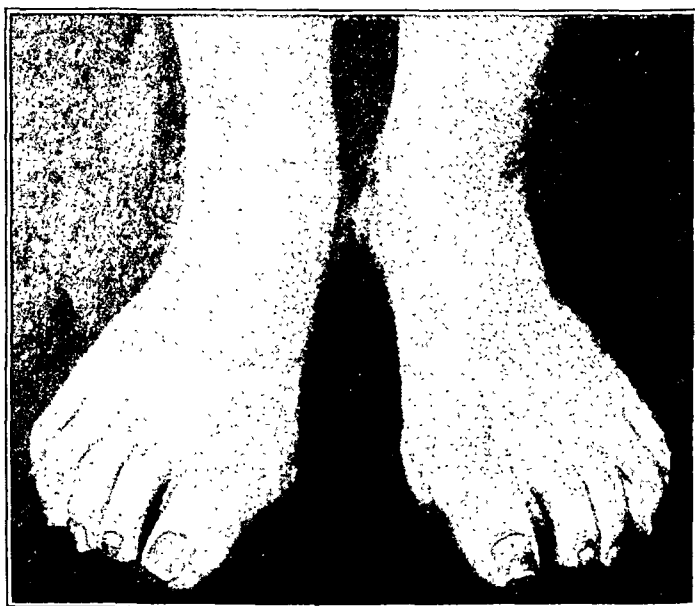


FIG. 4.—The broad feet in Case R (thyreoneural dystrophy).

The toes are clawlike, the fore part of the foot unusually wide (Fig. 4). Plantar stimulation elicits bilateral Babinski toe reflexes. The abdominal reflexes are diminished on the left. The gait is unsteady, and the patient walks upon her toes (Fig. 5). The foot posture recalls the "dromedary foot"

of dystonia musculorum deformans. There is perhaps some unsteadiness beyond this, but it is hard to determine. As has been noted, there is no Romberg. She can walk flat-footedly, but this is difficult, seems unnatural for her, and increases the unsteadiness of gait.

Such was the status of R. from 1921 to early 1923. Since that time she was observed over shorter or longer periods on five other occasions, namely, in July, 1923, December, 1924, March, 1925, August, 1927, and July, 1928. Brief reference will be made only to the *changes* occurring in her status.

In July, 1923, the following note was made: R. shows choreodystonic movements, affecting the shoulder and neck mainly, less evident in the lower extremities. There is marked up and down, and side-to-side movements of the head, and an almost constant rhythmical movement of pronation and supination while the hands are at rest. This recalls the tremor of

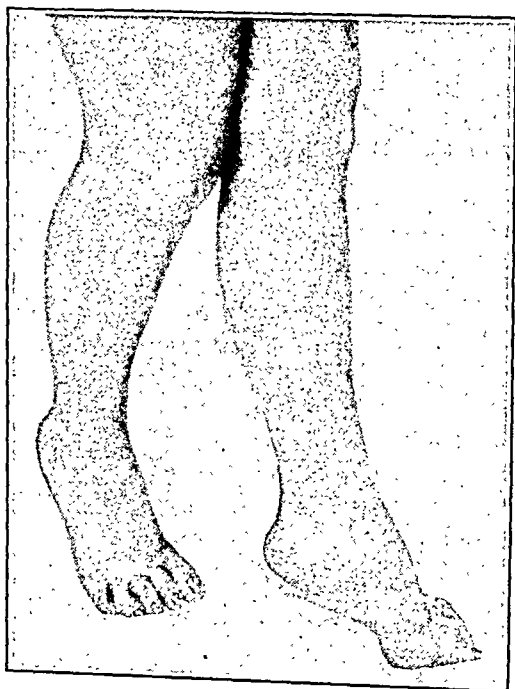


FIG. 5.—The tip-toe gait in Case R (thyreoneural dystrophy).

Parkinsonism. It is more marked on the right than on the left. There is a slight tendency toward flexion contracture in the fingers of the right hand. Hypotonia is present.

The left foot shows a typical equinovarus with extension of the first phalanges and flexion of the others; the right exhibits less marked extension of the first phalanges. There is a definite Babinski reflex on the left. The movements, especially the attitudinizing, are very reminiscent of Huntington's chorea.

Mentally, R. shows evidence of real intellectual defect. She answers all the questions in the ten-year-old scale, and almost all in the twelve. She has a mental age of eleven and a half years. She shows slight difficulty in retention. Her judgment is fairly good. Her associations are also fairly well executed. She shows no psychotic trends. Her emotional reaction is somewhat inadequate and excessive, but she shows no real evidence of conversion hysteria.

All other symptoms are the same but more marked. Diplopia is said to be associated with headaches. Occasional dysphagia is present with

regurgitation of food through nose and mouth. Recently dysuria has appeared. The spinal fluid is normal.

In December, 1924, generalized choreiform movements were noted, mainly on the right. Adiadochokinesis and rebound phenomena gave evidence of disorders of synergy in both upper extremities, more so on the right. The *R. Q.* was 0.78, 0.79. Basal metabolism was -18, -26.

By March, 1925, the continued thyroid therapy had caused some reduction in size of the thyroid. Its consistency was firmer. The movements, gait, feet, and so forth were the same. In addition, the muscles of the right corner of the mouth twitched slightly, and there were occasional movements of the lower jaw to the left. The entire head from time to time moved to one side, more to the right, with visible contractions of the sternocleidomastoid muscles. There were frequent arrhythmic-movements of the right shoulder and flexor movements of the hand. The entire body seemed to take part in these irregular movements.

In August, 1927, a depression of mood had set in, with much nausea and frequent vomiting. In addition to the above-mentioned movements, comment is made on a constant rhythmic movement of the right upper and lower extremities, of a Parkinsonian nature. Occasionally the amplitude increases markedly and the arm alternately flexes and extends at the elbow. The fingers are held flexed at the phalangeal joints. The thumb is adducted and flexed, and at times assumes the Parkinsonian attitude. The small finger is attitudinized in adduction and flexion. Occasionally, clonic movements of individual muscle groups are noted. Especially the toes of the right foot show rhythmic movements. There is alternate hypertonia and hypotonia, especially on the right side. The movements are very much exaggerated upon emotional disturbance.

In July, 1928, fits of crying and depression were noted. The choreiform movements were still more widespread. A bruised, torn condition of the external urinary meatus was the cause of the dysuria she complained of. The "fainting" attacks continued. *R. Q.* was 0.76, 0.75. Basal metabolic rate was -25 and -27.

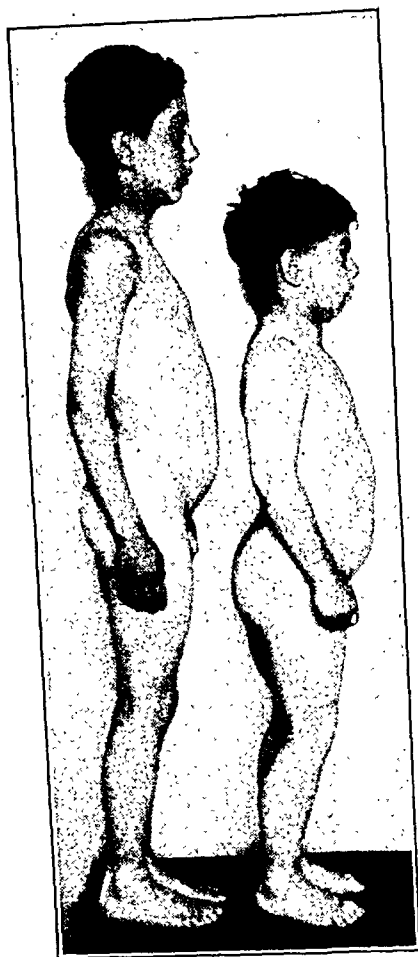
Disturbing dreams (pursuit by strange men, daggers thrust into her, and so forth) indicated conflicts associated with high-grade emotional tensions. An attempt at psychoanalysis earlier in her illness (1921) had been of no avail.<sup>1</sup>

**CASE II.—Development.** N., aged fourteen years. Of this case, not so much can be said. Birth was normal. He did not sit up until the age of four years, could not stand until the age of five and a half years, and did not talk until the sixth year. The anterior fontanelle closed at the age of three. N. is extremely backward in school. He can read and write simple sentences and can add simple figures, but cannot multiply. He is very quiet at home, sits about, has no initiative, is dull and acts slowly.

**History of Neural Defects.** These are few. He laughs in rather silly fashion without provocation (mental defect). There is fecal and urinary incontinence.

**Examination.** 1. *General.* He is a cretin in appearance (Fig. 6B), much shorter than his brother, who is three years younger (Fig. 6A). There are no gross defects of development (hernias, etc.), but the hair on the back is abundant above the scapulæ. The hands are spadelike. The feet are deformed, namely, a moderate degree of pes cavus and slight extension of the proximal joints of the toes, with flexion at the distal (compare his foot, Fig. 7B, and that of his brother, aged eleven years, Fig. 7A). Also

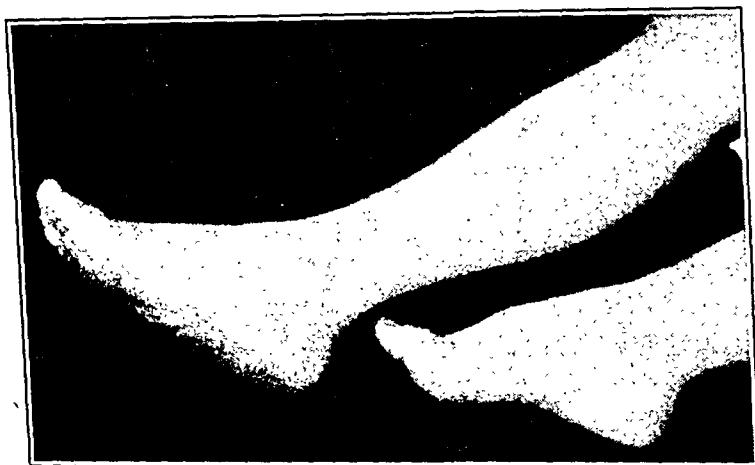
<sup>1</sup> In May, 1929, the right lobe of the thyroid gland had enlarged to the size of a small orange. It interfered somewhat with breathing and surgical intervention was being considered.



A

B

FIG. 6.—Case N (B) contrasted with his brother (A) three years younger.



A

B

FIG. 7.—Contrast between the pes cavus of Case N (B) and his brother's normal foot (A).

compare with the foot of R., Figs. 3 and 4). There is the same abnormal width of the fore part of the foot as in R. Clawing of the toes is not noticeable. Tightness of the Achilles tendon limits dorsiflexion of the feet.

. The teeth are abnormally spaced. The central incisors are very wide ( $\frac{1}{2}$  cm.), while the space between them is about 4 mm. The teeth are poorly developed and much decayed. The tongue is not unusually large. The fauces and tonsils are normal. The heart, lungs and abdomen are negative. The form of the body shows an increased lumbar curvature with pot belly. The genitals are normal. The thyroid is slightly enlarged and soft. Both the isthmus and lateral lobes are easily palpated. The skin is dry. No pubic or axillary hair is seen. The hair of the head is dry and coarse. The eyebrows meet; over the temples a fine growth of hair almost reaches the lateral ends of the eyebrows.

2. *Neural. Cranial nerves:* Negative. *Sensation:* Normal. There is no ataxia or Romberg. *Reflexes:* Normal except in the toe reactions. On stimulation of the sole of the foot, there is either dorsiflexion of the great toe or no movement at all. The dorsiflexion is more often obtained on the left than on the right. The foot then recalls that of Friedreich's ataxia. It is interesting to note that the left side is more affected in R. When the patient is supine, both great toes are extended, the left more so than the right. One feels that the absence of erectness permits the reaction to appear more readily, indeed, spontaneously. When the left thigh is forcibly flexed, there occurs extension of the great toes on the left, but not on the right. When the test is tried on the right, extension occurs as before, on the left, and not on the right (crossed Babinski). Fanning of the toes is observed on the left, not on the right. Gordon and Oppenheim reflexes are not elicited; indeed it is interesting to note that extension of the great toe on the left first increased by flexion of the ipsilateral thigh and then by flexion of the contralateral thigh, is changed to flexion by both the Gordon and Oppenheim tests. The gait is waddling with small steps and a slightly broadened base. His speech is slow, pronunciation of words defective.

**Discussion.** *Family Occurrence.* Since congenital myxedema or cretinism is well known to occur in families, it is not surprising to find associated neural signs in 2 of a family of 7.

*Etiology.* 1. The relation of thyroid insufficiency in the mother probably bears a very definite relationship to the occurrence of the myxedema and cretinism in her children. Furthermore, it is probable that the time of incidence of the greatest thyroid deficiency in the mother during her pregnancy has a bearing upon the development of the brain of the fetus, and the adequate nutrition of its cells. If the greatest insufficiency occur at a time when the basal ganglions, for example, are undergoing their greatest development, it would be natural to expect a defect in their development, and thus in their function. Furthermore, various grades of glandular defect may condition quantitatively different neural changes. The beneficial effect of thyroid therapy not only upon many cases of thyrogenic mental defect, but also upon many instances of the type here reported, indicates clearly the relationship of thyroid deficiency to cerebral development.

Another factor is insufficient maternal thyroid during the period of lactation. This is emphasized by McCarrison. He noted that his cases rarely showed signs until after lactation was, or should have been over, which he regards as evidence of deficient nutrition in general.

It would appear that the possibilities are these: (a) Insufficient maternal thyroid secretion during pregnancy with consequent neural defects in the offspring; (b) insufficient thyroid in the newborn uncompensated, due to insufficient thyroid in the maternal or other milk; (c) insufficient thyroid in the newborn, compensated for by the maternal milk. Such cases become hypothyroid after lactation is over.

In brief, therefore, deficient thyroid secretion during the critical periods of the development of the nervous system appears to be the cause of the disorders noted. Indeed, since Walter's experiments<sup>15</sup> show that the absence of the thyroid gland interferes with regeneration of peripheral nerves, it would seem that this gland influences the development of the peripheral, as well as the central nervous system.

2. The relation of the condition to infection has been discussed especially by Chagas,<sup>14</sup> who has maintained that his cases are dependent upon infection by the *Trypanosoma cruzi*. McCarrison believes it more likely that Chagas cases are primarily endemic cretinism or myxedema with secondary infection by trypanosomes. The cases here reported seem to bear out this contention. That intercurrent infections will aggravate congenital thyroid defect is well recognized, but it seems scarcely credible that a congenital thyroid defect in but 2 of 7 children could have been due to a chronic infection of the mother.

*Age of Onset and Recognition.* The age of recognition appears to be very early, as noted above, before the second year. The nervous symptoms may not be evident until late, as in the case of R. *The late onset of involuntary movements* in R. may be ascribed to one of two causes: First, a developmental abnormality of the basal ganglions due to a defective thyroid gland. The neural symptoms would be thus regarded as due to an abiotrophy comparable to that noted in Friedreich's ataxia. As a matter of fact, some of R.'s signs are reminiscent of that disease in which, also, the signs may not appear for a number of years after birth. Second, the work of Stern, Rapoport and Kremlew<sup>16</sup> shows that thyroid defect is associated with increased permeability of the blood—cerebrospinal fluid barrier for colloids. This would more readily permit the passage of toxic agents into the central nervous system of a hypothyroid individual. If this hypothesis be held, then an independent toxic-infectious agent may have been the causative factor for the neural phenomena in the case of R. This second theory would also explain the nonbeneficial effect of thyroid therapy in her case.

*Sex.* There is no sex limitation.

*Relation of Neural Symptoms to the Thyroid Deficiency.* The relation of the severity of the neural symptoms to the degree of glandular deficiency may vary greatly. As McCarrison has emphasized, in some cases, the myxedema is scarcely recognizable.



The effect of thyroid therapy upon the neural symptoms also may give evidence of this variability. In the two cases reported here, N. shows much more evidence of thyroid defect and much less evidence of neural disorder than R. Since N. has received relatively little thyroid therapy while R. has received a good deal over a long period, it is natural that she should show less endocrinic defect.

**Mental State.** The mental state requires little comment. It may vary from idiocy to almost no defect.

**Paroxysmal States.** These are extremely interesting and recall very closely those described by Ramsay Hunt<sup>17</sup> as static seizures. His description follows: "By static seizures I mean a form of epileptic seizure characterized by sudden loss of postural control." There is a brief loss of consciousness. Hunt states that he has only observed these fits in cases of idiopathic epilepsy. Here we have another disease in which static fits occur. They have also been seen in a case which, for want of a better name, may be designated as a striopyramidal syndrome. The partial loss of postural control in some cases of epidemic encephalitis of the Parkinsonian variety probably also belongs in the group of "static fits."

**Diplegia, Chorea, Ataxia, Torticollis, Facial Spasm.** Spastic diplegia has been the common finding in these cases—all grades from slight reflex changes to scissor-leg deformities. In neither R. nor N. was diplegia present; though in her gait R. now gives the impression of spasticity. The other choreiform and ataxic types seem less common. Though showing no evidence of being ataxic, R. gives that impression, due to her choreiform movements. Both cases show pathologic reflex changes (great toe), and foot deformities.

The choreic movements of R. are not unexpected in a group of cases some of which show typical diplegia, some chorea, and some ataxia. The association of stuttering with these movements has been noted. Her speech is like her movements, which are undoubtedly due to disease of the extrapyramidal systems. The unilateral onset followed later by bilateral involvement indicates progress of the condition in spite of fairly consistent thyroid therapy. In the cases of McCarrison, Langmead and Crookshank, improvement and even cure was noted under thyroid therapy. Obviously, the lack of thyroid plays a great part.

**Stuttering.** The stuttering brings up an intricate problem. This speech defect is so often attributed to functional disorders that the organic origin has been too little emphasized. It is probably true that a predisposing organic substrate, often familial, exists, even where the functional element predominates. We know now that careful search into the history of apparently exclusively hysterical conditions reveals a slight but definite history of organic disorder sufficient to cause the deviation of the functional disorder into a particular, definite groove. In R. it unquestionably was of organic origin. Its clear association with the spasmodic movements of the

face, trunk and extremities indicates a common basis. Such stuttering has been observed in other disorders clearly of organic nature, particularly in certain cases of epidemic encephalitis of the Parkinsonian variety.

**Foot Deformities.** The foot deformities have been of interest. What seems striking is the resemblance to the foot of Friedreich's ataxia. But even more striking is the fact that the deformities of the foot are due to overactivity of the intrinsic ventral muscles (pes cavus, and flexion of the toes at the proximal joints). The "ventral foot"<sup>18</sup> is common to many diseases, among which is diplegia. In a great number of diseases, one of which is here described, there is simply a release of a group of muscles having a definite common reaction. For a discussion of this matter *in extenso*, the reader is referred to other papers by Kraus.<sup>19</sup> What seems of greatest interest is that such deformities may occur as isolated, fragmentary manifestations of any of the forms of diplegia.

**Babinski Sign.** The occurrence of dorsiflexion of the great toes—a Babinski response in both cases, is striking, and recalls the findings of Chagas and McCarrison, who noted all degrees of involvement, from slight reflex changes to scissor-leg deformity. The dorsiflexion of the toes, like the foot deformities, represents a fragment of a more widespread condition.

**Constipation and Enuresis.** Constipation has been a conspicuous symptom throughout the observation of R. and has been very severe and resistant to treatment. It has been observed in these cases by McCarrison. Enuresis and frequency is present in N. and the latter in R. McCarrison has also noted enuresis. Its presence is probably related to the frequency. The origin of these symptoms may be in the hypothalamic regions of the brain. We would attribute them to a fairly extensive involvement of the central gray matter. They occur in epidemic encephalitis as well.

**Hyperaffectivity.** The functional element was considered of great, if not sole importance in the genesis of the stuttering and choreiform movements by others who first observed R. An attempt at re-education and a brief course of psychoanalysis have left R. worse than before.

Surely, the foot deformities, constipation, enuresis and Babinski sign are not to be considered of functional origin.

**Pathologic Anatomy.** (a) From the clinical findings, we may presume that the cerebral cortex in some part is affected. The disorders of neuromuscular control, chorea, athetosis, static fits, rigidity and ataxia suggest involvement of the basal ganglions and perhaps the cerebellum. Nystagmus and stuttering are no doubt infracortical in origin. The enuresis and constipation may also be due to disease of the central ganglions (namely, central origins of the visceral nervous system). (b) Weygandt<sup>20</sup> noted degenerative lesions of the nerve cells, leptomeningitis and perivascular leukocytic

infiltration, but he did not consider these specific. In three cases of hypothyroidism with mental disorders, Brun and Mott,<sup>21</sup> and Mott,<sup>22</sup> found generalized chromatolysis in the entire nervous system. This chromatolysis did not spare any special group of cells; however, the autonomic bulbar nuclei (vago-glossopharyngeal), the cerebro-spinal motor neurones and the sympathetic system were especially involved.

Both these authors and Weygandt found vacuolization of nerve cells, globular and "rapetissées" forms, excentricity of nuclei, as well as slight changes in the fibrils of the small pyramidal cells and those of Betz.

Marie, Trétiakoff and Stumfer<sup>23</sup> found marked deposits of iron and very little calcium in the walls of the bloodvessels of the cerebellum and striatum, especially in the globus pallidus. Intimal thickening was present, and even produced an obliterating endarteritis. As they state, their material was not very well fixed and could not be used for finer staining. The very small amount of calcium and large amount of iron in a woman of thirty-six does not suggest arteriosclerosis at all. Since iron is concerned in oxidation processes, these authors suggest that the lowered oxidation rate of hypothyroidism may have caused this deposit of iron.

Edmunds<sup>24</sup> found profound changes in the cells of the spinal cord, medulla, cerebellum (Purkinje cells) and cortex (medium and large pyramidal cells) with chromatolysis to total destruction, in thyro-parathyroidectomized dogs and cats. The calcium of the brain was one-half normal. Eaves and Croll<sup>11</sup> in the case above mentioned, found chromatolysis of nerve cells and accumulation of fatty granules in most regions, especially marked in the sympathetic ganglia. There was complete chromatolysis in the cerebral cortex, and the pyramidal tracts were so poorly myelinated as to suggest the fetal status, although the patient was fourteen years of age. Dye<sup>25</sup> examined the brains of thyroidectomized animals and found cell changes which were not specific. The "chromatolysis" was also found in tetany and fatigue states.

**Treatment.** This depends upon thyroid gland administration and general nourishment. In infants, the quantity of the mother's milk should be watched as well as her condition in regard to thyroid secretion. Beyond this, an attempt should be made to eliminate intestinal parasites and any chronic infection.

**Conclusions.** The condition may be defined as thyroneural dystrophy. It is a familial and probably congenital disorder of neuromuscular control of central origin, consisting of any or all of the following: chorea, athetosis, static fits, rigidity, ataxia, abnormal reflex changes, postural defects, and signs referable to disturbed function of the vegetative nervous system associated with a variable degree of mental and thyroid defect. The condition may be so

severe as to imitate precisely advanced cases of cerebral diplegia. Nystagmus, squint and stuttering may be present.

No specific pathology is known beyond changes in the internal structure of the cells of the nervous system and a deposit of calcium and iron about the bloodvessels.

It seems probable to us that there is a common but unknown cause of both the thyroid and neural dystrophy. It is well-known that a normal thyroid gland is necessary for the development of a normal central nervous system; hence, when thyroid gland is administered early in cases of thyro-neural dystrophy, the disorders due to the thyroid defect during growth may disappear. In this type of case, thyroid-gland administration is apt to be most beneficial.

Reference is made to the possibility of a superimposed toxic-infectious neural involvement due to the letting down of the blood—cerebrospinal fluid barrier for colloids, in consequence of the thyroid insufficiency. Such an hypothesis may explain the late appearance of the nervous symptoms and the ineffectiveness of thyroid therapy.

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## THE INTRAVENOUS USE OF GELATIN SOLUTION IN HEMORRHAGE.

(AN EXPERIMENTAL STUDY.)

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Low blood pressure due to hemorrhage is most adequately controlled by the direct transfusion of whole blood. There are occasions of sudden severe bleeding in surgical practice that demand immediate combative treatment with a substitute intravenous solution, available and efficient to elevate the blood pressure. The solutions commonly favored are saline, glucose and gum acacia. It is a frequent observation that these solutions have not proven altogether satisfactory, mainly because of their failure to sustain a high blood-pressure level over a prolonged period of time.

With the object of finding a colloid solution that will both elevate and maintain the blood pressure after hemorrhage, a series of experiments on rabbits was conducted with the results herewith presented.

**Procedure.** The technique employed was the same throughout all the experiments. Healthy rabbits of about 2 to 2½ kg. were anesthetized. The animals were bled from the right femoral artery by

introducing a cannula connected with an aspirating syringe, and the blood withdrawn in definite amounts necessary to produce a decreased blood pressure. The solution under study was then slowly injected into the right internal jugular vein. The blood pressure tracings were recorded on an electrokymograph by introducing into the right carotid artery, a cannula connected with a rubber tube attached to a mercury manometer.

The refractive index and a red blood-cell count were determined before and after each blood letting.

*Preparation of Stock Solution of Gelatin.* Fifty grams of "Difco" gelatin, 1 gm. of sodium carbonate and 0.9 gm. of sodium chlorid were placed in a flask containing 400 cc. of distilled water and boiled for fifteen minutes.\* This solution was filtered through glass wool and autoclaved for one hour at 252.2° F.; then permitted to cool and solidify. For use the gelatin in the flask was warmed, to which was then added 600 cc. of sterile distilled water, and the whole heated to a temperature of 98.6° F.

This stock solution was cultured for bacterial growth under aërobic and anaërobic conditions. Tests for toxicity were made by injecting 10 cc. of this solution into the veins of rabbits for six consecutive days. Though the animals were carefully watched for any untoward symptoms, there was no evidence of intravascular clotting or other ill effects, for these animals were subjected to further experiments and the organs, when examined after death, were found to be normal. Bayliss,<sup>1</sup> in "Intravenous Injection in Wound Shock" says that an unwelcome property of gelatin is that of causing intravascular clotting. No intravascular clotting was obtained with our stock gelatin solution.

The results were compared with other solutions, namely: 0.9 per cent saline, 5 per cent dextrin, 5 per cent starch and 2½ per cent gelatin.

*Experiment 1.—0.9 Per Cent Normal Saline Solution—Refractive Index 1.3340.* From a normal rabbit weighing 2 kg., with a blood pressure of 90 mm.Hg., a refractive index of 1.3480, 28 cc. of blood was removed. The pressure dropped to 40 mm.Hg., where it remained.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal	90	4,700,000	1.3480
On withdrawal of 28 cc. blood	40	2,600,000	1.3480
Two minutes after injection of 25 cc. normal saline	58	2,600,000	1.3480
Ten minutes after injection of 25 cc. normal saline	40	2,610,000	1.3480
Five minutes after injection of 20 cc. 5 per cent gelatin	85	2,608,000	1.3440
One hour after injection of 50 per cent gelatin	80	2,610,000	1.3450

\* The gelatin is heated in the presence of sodium chlorid and sodium carbonate to prevent decomposition, loss of viscosity and hemolysis of red cells.

Two minutes after the injection into the right internal jugular vein of 25 cc. of normal saline solution, the blood pressure rose to 58 mm.Hg., where it remained ten minutes before dropping to 40 mm.Hg.

Twenty cubic centimeters of 5 per cent gelatin solution was then injected intravenously. The blood pressure mounted to 85 mm.Hg., retaining for several hours a level of 80 mm.Hg.

*Experiment 2.—5 Per Cent Dextrin—Refractive Index 1.3420.* From a healthy rabbit weighing 2 kg., with a blood pressure of 90 mm.Hg., a red cell count of 5,400,000 per c.mm. and a refractive index of 1.3480, 30 cc. of blood was removed and the blood pressure dropped to 45 mm.Hg.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal . . . . .	90	5,400,000	1.3480
On withdrawal of 30 cc. blood . . .	45	2,800,000	1.3480
Five minutes after injection of 30 cc. 5 per cent dextrin . . . . .	65	2,810,000	1.3450
Sixty minutes after injection of 5 per cent dextrin . . . . .	65	2,806,000	1.3450
Ninety minutes after injection of 5 per cent dextrin . . . . .	65	2,816,000	1.3480
Three hours after injection of 5 per cent dextrin . . . . .	40	2,820,000	1.3480

Thirty cubic centimeters of warm 5 per cent dextrin solution was immediately injected. The blood pressure rose to 65 mm.Hg., and the refractive index registered 1.3450, remaining the same at the end of an hour.

Ninety minutes after the injection, however, the refractive index of the blood was back to normal while the blood pressure still registered 65 mm.Hg. Three hours later the animal died.

*Experiment 3.—5 Per Cent Starch Solution—Refractive Index 1.3390.* From a rabbit weighing 2.5 kg., with a blood pressure of 110 mm.Hg. and a refractive index of 1.3456, there were withdrawn 18 cc., 17 cc. and 15 cc. of blood, making in all a total of 50 cc., reducing the blood pressure to 50 mm.Hg.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal . . . . .	110	4,960,000	1.3456
On withdrawal of 18 cc. blood . . .	70	4,100,000	1.3456
On withdrawal of 17 cc. blood . . .	65	3,800,000	1.3456
On withdrawal of 15 cc. blood . . .	50	2,900,000	1.3456
Five minutes after injection of 30 cc. 5 per cent starch solution . . . . .	80-85	2,910,000	1.3410
Sixty minutes after injection of 30 cc. 5 per cent starch solution . . .	30-35	2,900,000	1.3430

Thirty cubic centimeters, of warm 5 per cent starch solution was slowly injected, sending the blood pressure immediately up to 80 to 85 mm.Hg. Twenty-five minutes later it had fallen to 35 mm.Hg.

Twenty-five cubic centimeters of warm 5 per cent starch solution was again injected intravenously, with no resulting rise in blood pressure. The animal died one hour later.

*Experiment 4.—2.5 Per Cent Gelatin Solution—Refractive Index 1.3360.* From a rabbit weighing 2.5 kg., with a blood pressure of 110 mm.Hg. and a refractive index of 1.3480, 40 cc. of blood was withdrawn, reducing the blood pressure to 48 mm.Hg.

Upon the injection of 40 cc. of warm 2.5 per cent gelatin solution, the blood pressure rose to 105 mm.Hg., where it remained for thirty-two minutes and then gradually declined to 60 mm.Hg.

Another injection of 20 cc. of 2.5 per cent gelatin solution elevated the blood pressure to 85 mm.Hg., where it remained for twenty minutes before it gradually fell. The animal died one hour and thirty-five minutes later.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal . . . . .	110	5,400,000	1.3480
Five minutes after withdrawal of 40 cc. blood . . . . .	48	2,000,000	1.3480
Four minutes after injection of 40 cc. 2.5 per cent gelatin . . . . .	105	2,100,000	1.3420
Thirty-two minutes after injection of 40 cc. 2.5 per cent gelatin . . . . .	60	2,100,000	1.3445
Five minutes after second injection of 20 cc. 2.5 per cent gelatin . . . . .	85	2,000,000	1.3420
Thirty minutes after injection of 20 cc. 2.5 per cent gelatin solution . . . . .	70	2,000,000	1.3440
Eighty minutes after injection of 20 cc. 2.5 per cent gelatin solution . . . . .	45	2,000,000	1.3470

*Experiment 5.—2.5 Per Cent Gelatin Solution—Refractive Index 1.3360.* From a normal rabbit weighing 2 kg., with a blood pressure of 75 mm.Hg. and a refractive index of 1.3480, 30 cc. of blood was withdrawn, reducing the blood pressure to 40 mm.Hg.

	Blood pressure, mm.Hg.	Red blood cells, per c.mm.	Refractive index.
Normal . . . . .	75	5,200,000	1.3480
Four minutes after withdrawal of 30 cc. blood . . . . .	40	3,710,000	1.3480
Five minutes after injection of 25 cc. 2.5 per cent gelatin solution . . . . .	45	3,520,000	1.3420
Twenty minutes after injection of 25 cc. 2.5 per cent gelatin solution . . . . .	30	3,550,000	1.3440
Second injection of 20 cc. 2.5 per cent gelatin solution . . . . .	40	....	1.3420
Thirty minutes after injection of 20 cc. 2.5 per cent gelatin solution . . . . .	40	3,540,000	1.3475



from a 45 to a 65 mm.Hg. reading, but it was not maintained for any length of time. The elimination of the dextrin solution appears to have set in after one hour, as indicated by the rise in the refractive index.

Starch solution produces a quicker reaction than dextrin, but is followed by a more rapid decline. The early elimination of the starch is indicated by the rise in the refractive index, occurring within one hour.

In our first experiments with gelatin we used a 2.5 per cent solution as advocated by Hogan,<sup>2</sup> but failed to obtain prolonged elevated blood pressure. Bayliss gives the probable cause for this failure and states that 6 per cent gelatin gives permanent results.

As demonstrated by further experiments, the use of a 5 per cent gelatin solution showed that not only can the blood pressure be restored to the original height and above it, but that it can be maintained at that level for many hours. That this is due to the persistence of the gelatin solution in the circulating blood is borne out by the change in the refractive index, which in our experiments decreased after the injection of gelatin, and remained at that lower level for several hours. Since the rise of the refractive index was not concomitant with a drop in the blood pressure, it is possible that the gelatin still remained in the circulation.

Our experiments have impressed us with the favorable effect of the injection into the blood stream of a 5 per cent gelatin solution.

**Conclusion.** Intravenous injection of 5 per cent gelatin solution into animals with low blood pressure due to hemorrhage restores the blood pressure for several hours. The continued presence in the circulation of the gelatin solution is indicated by the low figure reached and maintained by the refractive index. Solutions of weaker concentration are not as effective.

No untoward effects of gelatin were demonstrated in the animals under experiment.

Solutions of saline, dextrin and starch elevate the blood pressure, but fail to maintain the elevated level. The rapid elimination of these solutions is indicated by the quick return of the refractive index to normal.

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## REVIEWS.

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**PUBLIC HEALTH AND HYGIENE: IN CONTRIBUTIONS BY EMINENT AUTHORITIES.** Edited by WILLIAM HALLOCK PARK, M.D., Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College, and Director of the Bureau of Laboratories of the Department of Health, New York City. Second edition, thoroughly revised. Pp. 902; 123 illustrations. Philadelphia: Lea & Febiger, 1928. Price, \$9.00.

PREVENTIVE medicine has experienced remarkable advances in recent years, both in theory and application. Moreover, the "growing opinion that public health is to a large extent purchasable by effort and money, and that it is worth purchasing, has stimulated health authorities to develop their opportunities and to assume greater responsibilities." The new edition of Dr. Park's work, thoroughly revised and with new chapters on cancer control and on aseptic technique in the control of communicable diseases, covers well the great strides forward in our knowledge concerning hygiene and in the increasing scope of public health work. Twenty-four eminent authorities have contributed to make this a truly authoritative volume. The material is presented in a thoroughly practical manner, with thought particularly for medical officers, physicians and medical students. The Reviewer was impressed by the very small amount of reduplication of subject matter in chapters on closely related topics, although written by different men.

R. K.

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**THE LIFE OF HERMANN M. BIGGS, M.D., D.Sc., LL.D., PHYSICIAN AND STATESMAN OF THE PUBLIC HEALTH.** By C.-E. A. WINSLOW, DR. P.H., Professor of Public Health, Yale School of Medicine. Pp. 432; 35 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$5.00.

THOUGH many doubtless know of Hermann Biggs as an important factor for many years in the New York City Department of Health, probably few would rank him—as the London School of Hygiene and Tropical Medicine have publicly done—as one of the twenty-one who have done most to advance public health since the seventeenth

century. The reasons for such a choice become apparent on reading Doctor Winslow's sympathetically and pleasantly written narrative. More than a biography of a distinguished sanitarian, the book serves as a typical story of the development of modern public health. The accounts of the administrative control of tuberculosis, the spreading of diphtheria antitoxin, the combatting of other preventable diseases, in fact the demonstration that "health was purchasable," alternate with fascinating glimpses of an interesting and versatile personality that should recommend the book to all concerned with the health of the public.

E. K.

MANUAL OF PROCTOLOGY. By T. CHITTENDEN HILL, Ph.B., M.D., F.A.C.S., Instructor in Proctology, Harvard. Graduate School of Medicine. Third edition. Pp. 272; 86 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$3.50.

THE previous (second) edition of this useful and practical manual was reviewed in these columns three years ago. The present edition is practically identical with the former with the exception of the final chapter, which deals with cancer of the rectum. This has been written by Dr. E. Parker Hayden and is largely devoted to a description of the well-known Jones operation.

R. G.

AN INDEX OF DIFFERENTIAL DIAGNOSIS OF MAIN SYMPTOMS. By VARIOUS WRITERS. Edited by HERBERT FRENCH, C.B.E. (MILIT.), M.D., (OXON.), F.R.C.P. (LOND.), Physician to H. M. Household; Physician and Lecturer, Guy's Hospital; Consulting Physician to Queen Alexandra's Military Hospital, Milbank. Fourth edition. Pp. 1171; 701 illustrations (179 in colors). New York: William Wood & Co., 1928. Price, \$18.00.

THIS work needs no introduction to the medical public. Three previous editions and seven reprintings, as well as translations into Spanish and Italian, are sufficient evidence of its popularity. It is with delight, therefore, that we welcome the new fourth edition of the book after its being five years out of print. Written by twenty contributors, it is a treatise on the application of differential diagnosis to all the main signs and symptoms of disease, and covers the whole ground of medicine, surgery, gynecology, ophthalmology, dermatology and neurology. As in previous editions, the material is presented by articles on signs and symptoms, alphabetically arranged, with a discussion of the methods of distinguishing between

the various diseases in which each symptom may occur. A most valuable feature is an index of amazing completeness—225 pages with more than 90,000 page references—in which the symptoms, in addition to being singly listed, are gathered together under the headings of the various diseases. The proper use of the book, therefore, requires careful reference to the index as well as to the text. The illustrations are numerous and well done. All physicians will find in this volume a most satisfactory and valuable diagnostic aid.

R. K.

DIABETES LATENTE. By DR. FELIX PUCHULU. Pp. 213. Buenos Aires: Talleres Gráficos Ferrari Hnos., 1929.

LATENT diabetes is here considered as preceding and separate from early diabetes; sugar tolerance is lowered, but glycosuria does not follow ingestion of carbohydrates. Demonstration of this state, perhaps together with some of the clinical symptoms, permits a diagnosis and installation of dietetic treatment similar to that of mild diabetes. Illustrative cases are given.

E. K.

A HISTORY OF THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY. By P. M. ASHBURN, Colonel, Medical Corps, U. S. Army. Pp. 448. Boston and New York: Houghton Mifflin Company, 1929.

"THE Medical Department of the United States Army has an enviable record which is little known to the general public. It has to its credit the conquest of yellow fever the elucidation of the process of gastric digestion, a prominent share in the reduction of communicable diseases, and many other notable achievements.

"This lucid, simple, unbiased account of its history deals not only with the story of the Medical Department from Revolutionary days to the present hour, but also with the general status of the Army as a whole and the condition of medicine in each period. No work like it has heretofore appeared."

This quotation on the paper cover of the book well indicates its scope and nature. As General Ireland states in his introduction, it is an interesting, true story, "documented and accurate, but not long drawn out or hard to read." Even the work of Reed, Gorgas and the Department in general during the World War is not sufficiently known by the medical and general public, still less is that of Senter of Quebec fame, Lovell in 1812, Beaumont and St. Martin, Billings and other officers of the department, who made valuable contributions to varied aspects of medical progress.

E. K.

PRINCIPLES AND PRACTICE OF ELECTROCARDIOGRAPHY. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 226; 61 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$7.50.

IN spite of the numerous books on electrocardiography that have recently appeared, chiefly dealing to be sure with clinical aspects, the author feels that there is still "need of a simple yet comprehensive treatise by an author who can reasonably lay claim to experience." Certainly Dr. Wiggers fulfills the latter requirement, and it may also safely be said that his book makes as good a presentation as can be found today of such matters as apparatus, technique, fundamental physical and physiological principles, etc. Slightly less than half the book is devoted to clinical interpretations and diagnosis. This is accurately written and sufficiently illustrated, though it may not be quite as useful for the clinical beginner as some of the more elaborately detailed works above referred to.

E. K.

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NOTES ON CHRONIC OTORRHEA, WITH SPECIAL REFERENCE TO THE USE OF ZINC IONIZATION IN THE TREATMENT OF SELECTED CASES. By A. R. FRIEL, M.A., M.D. (UNIV. DUB.), F.R.C.S.I., Assistant Aurist, School Medical Service, London County Council; Aurist to Tottenham, Hornsey, and Walthamstow Education Committees. Pp. 87; 54 illustrations. New York: William Wood & Co., 1929. Price, \$2.25.

THE subject and method of zinc ionization treatment for otorrhea is one with which every otologist should be familiar. Simple fundamental experiments followed by methods of clinical application, together with charted results by various experienced observers, emphasizes the importance, if not actual necessity in many cases, for this specialized treatment. Emphasis is placed on accurate diagnosis, proper classification of type of suppuration, barriers encountered and instruments demanded to meet the individual requirements. It is far in advance of the medicated "ear drops" method which has held sway for so many years.

D. H.

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DISEASES OF THE LIVER, GALL BLADDER AND BILE DUCTS. By SIR HUMPHREY ROLLESTON, BART, K.C.B., and J. W. McNEE. Third edition. New York: Macmillan Company, 1929.

THE review of the first edition of this work was written for this journal by Sir William Osler (May, 1905) and signed with the

initials E. Y. D., well known to the initiated. The opinion expressed then of the usefulness and value of the book has been thoroughly established. In this edition Sir Humphrey Rolleston has associated Dr. J. W. McNee, whose work on jaundice is well known. It may be said that this work is to be regarded as the best which we have on the subjects with which it deals and it is a storehouse of facts and references. The advances in our knowledge of hepatic and biliary disorders since the previous edition have been many, especially relating to jaundice, functional tests of hepatic disease and cholecystography. The discussion on cirrhosis has always seemed to the Reviewer to be especially clear. Throughout the book the orderly arrangement is a great aid to the reader. Altogether this work can be commended as the best discussion of the subject and one to which every student of hepatic and biliary disease must refer.

T. M.

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THE NEUROSES. By ISRAEL WECHSLER, M.D., Associate Professor of Clinical Neurology; Attending Neurologist to the Neurological Institute, The Montefiore and Sydenham Hospitals, New York City. Pp. 330. Philadelphia: W. B. Saunders Company, 1929. Price, \$4.00.

THIS is an expansion of a chapter from a larger work. The entire approach and classification is Freudian and bears the stamp of approval of the founder of that School. Psychasthenia is not grouped as such and epilepsy is not included. Thirty-two case reports illustrate, well, the author's viewpoint. Drugs are not ignored but one should not speak of luminal as a "mild hypnotic."

The value of *rest cures* are quite accurately gauged by their employment in exhausted, anemic and emaciated patients, while their usefulness is not seen in "neuroses rooted in mental conflicts over inner and outer situations."

An excellent addition to psychoanalytic literature.

N. Y.

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OSTEOMYELITIS AND COMPOUND FRACTURES. By H. WINNETT ORR, F.A.C.S., Chief Surgeon of the Nebraska Orthopedic Hospital. Pp. 208; 54 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$5.00.

THIS book is a presentation of the Orr method of treatment of infected wounds of the bones and joints which, in brief, consists of the free opening and removal of dead tissue, open drainage by sterile vaseline pack, maintenance of rest by the application of an extensive plaster-of-Paris cast, and omission of dressings for a matter of several weeks.

The clinical results obtained by the author and other surgeons in the west are remarkable and if like results are obtained generally, it will mean a decided advance in this field. The surgeons in the east who are now using this method are enthusiastic.

The book is written in a pleasing style, is well illustrated and worth owning. J. M.

TUMORES PRIMITIVOS DE LA PLEURA. By DR. JOSE W. TOBIAS. Pp. 479; 60 illustrations. Buenos Aires: El Ateneo, 1928.

THOUGH the book is divided into four parts (I, Endothelioma; II, tumors, malignant, benign and mixed; III, inflammatory tumors; IV, cystic tumors), the discussion of the first is much the most voluminous and profitable. The author believes that there is a true primary endothelioma of the pleura of connective-tissue origin, and that though bronchial carcinomata may closely simulate it, they can always be differentiated microscopically. Symptomatology, diagnosis and treatment are suitably discussed. Adenoma lipoma, chondroma, fibroma, mixed tumors, hydatid and dermoid cysts, tuberculosis, syphilis and actinomycosis receive more superficial treatment. E. K.

## BOOKS RECEIVED.

### NEW BOOKS.

*Esophageal Obstruction.\** By A. LAWRENCE ABEL, M.S. (LOND.), F.R.C.S. (ENG.). Pp. 234; 132 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$9.00.

*Annals of the Pickett-Thomson Research Laboratory. Volume IV.* November, 1928, Part I and April, 1929, Part II. The Pathogenic Streptococci. An Historical Survey of their Rôle in Human and Animal Disease.\* Pp. 494; 18 illustrations. London: Baillière, Tindall & Cox, 1929.

*The Cytoarchitectonics of the Human Cerebral Cortex.\** By CONSTANTIN VON ECONOMO. Translated by DR. S. PARKER. Pp. 186; 61 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$6.25.

*Diagnosis and Treatment of Deformities in Infancy and Early Childhood.\** By M. F. FORRESTER-BROWN, M.S., M.D. (LOND.). Pp. 199; 79 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$4.15.

*The Robert Jones Birthday Volume. A Collection of Surgical Essays.\** Pp. 434; illustrated. New York: Oxford University Press, American Branch, 1929. Price, \$13.00.

*The Autonomic Nervous System.\** By ALBERT KUNTZ, PH.D., M.D. Pp. 576; 70 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$7.00.

\* Reviews of titles followed by an asterisk will appear in a later number.

- Laboratory Manual of the Division of Bacteriology, Peking Union Medical College.\** Prepared under direction of C. E. LIM. Pp. 154. Peking, China: Peking Union Medical College Press, 1929. Price, \$1.50.
- Medical Clinics of North America, Boston Number*, July, 1929, Volume XIII, No. 1. Pp. 280; 36 illustrations. Philadelphia: W. B. Saunders Company, 1929.
- Mechano-Therapy.\** By MARY REES MULLINER, M.D. Pp. 265; 57 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$2.75.
- Progressive Medicine, Volume XI, June*, 1929. Pp. 389; illustrated. Philadelphia: Lea & Febiger, 1929.
- Surgical Clinics of North America (Mayo Clinic Number)*, August, 1929. Pp. 208; 72 illustrations. Philadelphia: W. B. Saunders Company, 1929.

## NEW EDITIONS.

- Diseases of the Larynx.* By HAROLD BARWELL, M.B. (LOND.) F.R.C.S. (ENG.). Third edition. Pp. 278; 112 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$3.65.
- Bodily Changes in Pain, Hunger, Fear and Rage.* By WALTER B. CANNON, M.D., Sc.D., LL.D. Second edition. Pp. 404; 43 illustrations. New York: D. Appleton & Co., 1929. Price, \$3.00.
- American Illustrated Medical Dictionary.* By W. A. NEWMAN DORLAND, M.D. Fifteenth edition. Pp. 1427; 525 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, plain, \$7.00; Thumb index, \$7.50.
- Herman's Difficult Labor.* Revised by CARLTON OLDFIELD, M.D. (LOND.), F.R.C.S. Seventh edition. Pp. 560; 105 illustrations. New York: William Wood & Co., 1929. Price, \$5.50.
- Artificial Sunlight and its Therapeutic Uses.* By FRANCIS HOWARD HUMPHRIS, M.D. (BRUX.), F.R.C.P. (EDIN.), M.R.C.S. (ENG.). Fifth edition. Pp. 340; 31 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$3.25.
- Ker's Infectious Diseases.* Revised by CLAUDE RUNDLE, O.B.E., M.D. (LOND.), M.R.C.S. (ENG.). Third edition. Pp. 614; 67 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$10.50.
- Hemorrhoids.* By ARTHUR S. MORLEY, F.R.C.S. (ENG.). Pp. 122; 10 illustrations. Fourth impression revised and enlarged. New York: Oxford University Press, American Branch, 1929. Price, \$2.00.
- The Treatment of Fractures and Dislocations in General Practice.* By C. MAX PAGE, D.S.O., M.S. (LOND.), F.R.C.S. and W. ROWLEY BRISTOW, M.B., B.S. (LOND.), F.R.C.S. Third edition. Pp. 284; 161 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$4.25.
- Tuberculosis. Its Prevention and Home Treatment.* By H. HYSLOP THOMSON, M.D., D.P.H. Third edition. Pp. 99. New York: Oxford University Press, American Branch, 1929. Price, \$0.75.
- The Principles of Electrotherapy and their Practical Application.* By W. J. TURRELL, M.A., D.M., B.CH. (OXON.). Second edition. Pp. 413; 34 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$4.75.
- Tweedy's Practical Obstetrics.* Edited and largely rewritten by BETHEL SOLOMONS, M.D., F.R.C.P.I. Sixth edition. Pp. 759; 294 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$7.50.

\* Reviews of titles followed by an asterisk will appear in a later number.



# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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AND

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**An Investigation of Various Factors which Affect the Sedimentation Rate of the Red Blood Cells.**—Probably because of the ease in which the test may be carried out rather than from any definite information which is given to the clinician, a very extensive bibliography on the sedimentation rate of the red blood cells in different types of disease has resulted. Two papers that have been recently published are of some interest in this connection. The first of these is by ROURKE and PLASS (*J. Clin. Invest.*, 1929, 7, 365). They studied various factors which may influence the sedimentation rate of the erythrocytes. These authors found that heparin is the ideal anticoagulant. The blood, if it stands longer than six to twelve hours, leads to a slowing of the rate, and rapid centrifuging of the blood does not affect its settling speed even after remixing. Blood dilution leads to a rapid settling of the cells. Aëration of venous blood does not seem to affect the rate of settling so that collection of blood under oil is not necessary. Increased changes in temperature make for more rapid sedimentation, but not within the range of ordinary room temperature. Ingestion of food seems to have slight, if any, effect, and the same statement applies to short, violent exercise.

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**Sedimentation Rate of Red Blood Corpuscles in Acute and Chronic Infections.**—WYLIE (*J. Infect. Dis.*, 1929, 45, 6) followed the method of Zeckwer and Goodell. She found that the average rate of sedimentation in all infections studied was below the normal average and differs somewhat in different conditions. The phenomenon is not influenced by the age of the patient nor by the height of the fever, and is probably dependent upon the amount of tissue destruction. Certainly in the case of tuberculous infection the resistance of the patient seems to play no part. Summing up the two papers, it may be seen that they corroborate the general feeling that in the test of the present day the rate

is not affected by gross factors such as age, sex, temperature, ingestion of food, exercise or other factors which might mitigate against the test as a clinical guide. On the other hand, the test indicates that there is something wrong with a patient, but does not by any means give any light as to what is the cause of the disturbance. If the patient is sick, this the test shows. Where, when, or how is not elucidated.

**Selective Action of Roentgen Rays on the Blood Cells of the Cat.**—The profound effects that radium and Roentgen ray have on the bone marrow have been proven often clinically. The severe anemia resulting from prolonged exposure to radio-active substances frequently becomes a type of aplastic anemia. WRIGHT and BULMAN (*Lancet*, 1929, ii, 217) show that the Roentgen rays have a selective action on the blood cells of the cat. If the dosage is varied, different results will take place. The important factors that are brought out are as follows: The lymphocytes are decreased early and markedly; the polymorphonuclears show an irregular initial increase with a slower and slighter degree of decrease than the lymphocytes; changes in the red blood cells occur still later; in nonfatal cases the anemia develops slowly and recovery is gradual and is paralleled by the platelet count; in fatal cases a severe acute anemia develops with evidence of hemolysis and widespread hemorrhage without the blood platelets being affected.

**Effect of Coffee and Tea on Gastric Secretion.**—GANTT (*J. Lab. and Clin. Med.*, 1929, 14, 917) states that the universal use of coffee and tea as beverages among civilized people is the reason why their action should be thoroughly understood. As a matter of fact, in many European countries the main water intake is disguised as tea or coffee. For these reasons he undertook and determined the chemical reaction on the stomach of coffee and tea when taken with food. A Pavlov preparation with the experimental animal was made. The dog then had his stomach washed out, and the bread and tea mixture was introduced through the gastric fistula. As a control on the alternate days, a bread-and-water mixture, equal to that of the tea, was given. Gantt found that the chemical action of the tea and bread was practically the same as the bread-and-water. The coffee-and-bread meal produced a slightly greater amount of gastric juice the first two hours. From this investigation it seems fair to conclude that even very strong coffee and tea affect the stomach secretions only through the nervous elements of the water content, there being no, or only slight, chemical influence from the tea or coffee.

**The Bacteriological Diagnosis of Whooping Cough.**—SUGARE and MCLEOD (*Lancet*, 1929, ii, 165) have made an investigation of the bacteriology of whooping cough. The work of Bordet and Gengou has been looked upon with considerable skepticism, certainly until the last few years, as to whether the etiologic organism *B. pertussis* is responsible for pertussis. They state that in England at least no attempt has been made to corroborate or reject the findings of the two French bacteriologists. By using a French preparation, Bordet-Gengou media, they were able to isolate the organisms in 12 out of 21 cases and in all the cases examined within the first week of the disease. *B. pertussis*

and *B. influenzae* are two distinct bacterial species, and while the latter organism was found quite frequently in the secretions from the upper respiratory tract of 50 children of ten years of age dying from other diseases than whooping cough, the *B. pertussis* was not found. They conclude quite definitely that the bacteriologic diagnosis of whooping cough is generally found to be easier and more exact than that of diphtheria and could be of practical service to the community.

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## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

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**End Results of Surgery of the Biliary Tract.**—CATTELL (*Ann. Surg.*, 1929, 89, 930) states that cholecystectomy is the operation of choice for gall stones and for acute and chronic cholecystitis and should be done except in the very poor risk. Cholecystectomy gives relief in a high percentage of patients with gall stones. Less than 30 per cent of patients in this series having cholecystostomy have been relieved over a long period of time. The operative treatment for the noncalculous gall bladder is not satisfactory except where there is definite pathology present and conspicuous clinical symptoms associated with it. The mortality after gall-bladder operations is shown to have been appreciably increased by doing other abdominal and pelvic operations at the same time. Such practice should be discouraged. The operative mortality in patients with common duct stones is high. In addition, a considerable number operated upon for this condition have recurrence of symptoms which result in a high subsequent nonoperative mortality. The early removal of gall stones will reduce the incidence of common duct stones, and for this reason should be urged. The mortality after operation on the gall bladder alone is very low. In the past two years no death has resulted after such an operation. Two deaths have occurred in the past 275 consecutive operations on the gall bladder and ducts exclusive of malignancy and stricture. Both were in patients with common duct stones. By increasing the incidence of common duct exploration from 15 to 20 per cent of all patients, the incidence of common duct stones has been raised from 8 to 12 per cent, an increase of 50 per cent. It is obvious that exploration of the common duct should be done more frequently than is generally practised. There is a group of patients with symptoms commonly attributed to the gall bladder, whose symptoms are due to functional disturbance of the colon. Failure to obtain relief after operations for chronic cholecystitis is usually due to incomplete or wrong diagnosis.

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**The Determination of Preoperative Indications for Correction of Bone Deformities.**—SCHWARTZ (*J. Bone and Joint Surg.*, 1929, 11, 385) writes that the correction of fixed angular and curved deformities of

the long bones almost invariably requires a solution of continuity. Osteoclasis has been supplanted by open reduction, which makes it possible to approach these problems by methods of precision. The method described emphasizes that decisions made at the operating table relative to the level and shape of section to be made for the correction of a given deformity, are not reliable. This is true because it has been graphically demonstrated that there is only one level and section of given shape which will result in the maximum correction of a given deformity. By this method the possibility of inducing other deformities is avoided. Pre-operative determination of the level and shape of section to be removed is, therefore, necessary for the greatest assurance of the most desirable end result from operation for the correction of angular and curved deformities in long bones.

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**Congenital Dislocation of the Knee.**—McFARLAND (*J. Bone and Joint Surg.*, 1929, 11, 281) says that this rare condition has been attributed to antenatal injury, wrong pull of muscles, malposition *in utero* and primary embryonic defect. The only theories worth considering are the two last, malposition and primary defect. Both causes may operate and the cases fall into two very distinct groups, according to their etiology. Those associated with other abnormalities, such as cleft palate, hare lip, cardiac lesions and spina bifida, are due to a primary embryonic defect. Such cases are not amenable to conservative treatment and an open operation to secure a mobile knee is advisable. The second group includes the cases in which the condition is unaccompanied by other serious defects. These are due to malposition *in utero* and respond to manipulation aided, perhaps, by subcutaneous tenotomy. In the cases of long standing a difficult problem has to be attacked. It would seem likely that a tenotomy of the anterior structures of the knee and an osteotomy of the femur and flexion at the osteotomy might give a useful knee.

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## THERAPEUTICS

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UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

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AND

SOMA WEISS, M.D.,

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**The Diet in Diabetes.**—VON NOORDEN (*Therap. d. Gegen.*, 1929, 70, 241) reports on his personal experiences with different diets in diabetes. He reviews the use of some of the diets which he employed years before the introduction of insulin. He believes that the administration of

the proper diet is more difficult in the presence of insulin than it is without it. It is not correct to assume that a unit of insulin always assimilates a definite amount of carbohydrate. The patient should follow a strict diet even if the disease is present in the mildest form. The diet should be planned for each patient individually. The neglect of this principle would be as much a mistake as the failure to apply early therapy in tuberculosis and cancer. The determination of the proper diet with or without insulin is especially difficult in ambulatory patients. Cases in which synthalin proved to be a good substitute for insulin could almost always be well managed without synthalin or insulin. The beneficial effect of foreign-body therapy with the administration of proteins is so far unproven.

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**The Choice of Anesthesia in Operations on the Thyroid.**—In the opinion of KONIG and STANNHKE (*Therap. d. Gegen.*, 1929, 70, 250), the application of local anesthesia in patients with nontoxic goiter is preferable unless the patients are below the age of twelve years or other specific contraindications exist. On the eve preceding the operations, the patient receives 10 to 20 mg. of pantopon or "dilaudid-scopolamin." The choice of anesthesia in cases with toxic goiter is difficult. The authors appreciate the lack of unanimous opinion by leading surgeons. They, nevertheless, prefer ether narcosis in patients with toxic goiter.

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**The Use of Sedatives in Labor.**—The important part played by sedatives in modern obstetrics is emphasized by FAIRBAIRN (*Brit. Med. J.*, 1929, i, 753). Fatigue is one of the most important factors interfering with normal delivery. Whenever, especially in the early stage of labor, the woman is worried and fatigued, and there are signs of irregular uterine contractions, a liberal dose of some sedative should be given and repeated if necessary. Morphine in doses of  $\frac{1}{4}$  to  $\frac{1}{2}$  grain may result in beneficial effect. The purpose of morphine-hyoscin narcosis is not analgesia or anesthesia, but amnesia. The successful induction of amnesic narcosis removes almost entirely the inhibitions of uterine action of emotional and psychic origin. It also lessens the fatigue. Reflex response to stimuli augmenting the strength of contractions may be diminished under this narcosis. It should be limited, therefore, to cases in which the exclusion of fatigue and inhibitory influences plays a more important rôle than the decreased reflex response. The "twilight sleep" should be given soon after rhythmical labor pains are definitely established, provided the patient is "prepared." The patient should be isolated from noise and light. An initial dose of  $\frac{1}{4}$  grain of morphine with  $\frac{1}{150}$  grain of hyoscin should be given, followed at hourly intervals by  $\frac{1}{450}$  grain of hyoscin. In general, the standard dose should be increased in first labors, for big women of strong physique, and for imaginative, oversensitive and nervous patients. Idiosyncrasies for hyoscin must be watched for. A memory test should be applied to determine the state of amnesia. Flushing of face and dilatation of pupils are not necessarily indications of overdosage. With overdosage of hyoscin, the pulse rate shows marked rise and the respirations a marked fall. If the patient is unable to empty her bladder, a catheter should be used. Important is the continuous observation of the patient

by a skilled nurse. In the second stage of labor there may be indications for falling back on a light general anesthesia, especially once the outlet begins to gape, and birth is imminent. Sedatives should be given to patients in whom a long and tedious labor may be anticipated. The problem of relief of pain of labor and the saving of nervous strain without interfering with the normal function of delivery is still unsolved.

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## PEDIATRICS

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UNDER THE CHARGE OF  
THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

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**Typhoid Fever in Children.**—HALPERN (*Am. J. Dis. Child.*, 1929, 38, 10) studied 67 children ill with typhoid fever, with an age range of from ten months to twelve years. He noted that the onset was relatively abrupt in almost one-half of the cases. Abdominal pain was a frequent initial complaint, and because of its location at times in the right lower quadrant and the sudden onset with vomiting it occasionally made difficult the exclusion of acute appendicitis. Signs of meningeal irritation were relatively frequent, and often the disease with this complication simulated the picture of a true primary meningitis. The pulse rate was rapid and in proportion to the degree of the fever in one-fourth of the cases. The blood in 6 per cent of the cases showed a leukocytosis in the absence of complications instead of the usual leukopenia. Positive Widal reactions outnumbered the positive blood cultures and both were more frequently obtained during the second week of the illness. The stools gave a higher percentage of positive cultures than the urine. The complications were usually suppurative processes. Death occurred most often in the second week of the illness. Signs of meningeal involvement often preceded death.

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**Comparative Effects of Diphtheria Toxoid and Toxin-antitoxin as Immunizing Agents.**—WEINFELD and COPPERSTOCK (*Am. J. Dis. Child.*, 1929, 38, 35) record their experiences with toxoid in the active immunization against diphtheria. In a well controlled group of 104 adults with positive reactions to the Schick test, it was found that in 83 or 92 per cent of 89 that were treated with two doses of 1 cc. each of toxoid, the reaction became negative. Of 15 persons receiving one dose of 1 cc. of toxoid, the Schick reaction was also rendered negative in 7 or 46 per cent. In the routine employment of the Schick test, certain sources of error were noted. The majority of the subjects comprising this series came from rural districts. A high incidence of positive reactions to the Schick test, 73 per cent was found in this group, and this high incidence stands in interesting contrast to the low proportion of

persons susceptible to diphtheria found in well populated areas. The interesting phenomenon of reactions to the administration of toxoid was studied. While in a general way it was found that local reactions to toxoid were much less frequent as compared with those following toxin-antitoxin, general reactions to toxoid were observed with greater frequency. It was noted that both local and general reactions to toxoid were rare in children. Studies on the nature of these reactions to the toxoid tend to indicate that allergy plays an important part in their manifestations. The high incidence of reactions to toxoid in persons presenting both a history of allergy and a pseudoreaction to the Schick test was particularly striking. The use of antitoxin entails the possibility of the production of sensitization to horse serum, whereas with the use of toxoid this possibility is obviated. The authors feel from their experience that toxin-antitoxin is inferior as an immunizing agent to toxoid. The relatively greater stability, innocuousness, and need for fewer injections of toxoid are additional advantages.

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**Congenital Pyloric Obstruction.**—MOORE, BRODIE, DENNIS and HOPE (*Arch. Ped.*, 1929, 46, 416) remind us that congenital pyloric obstruction has shown a very rapid increase in the past forty years. The statistics show that 2.7 per cent of all infants under one year of age suffer from this disease. Dietary habits may be responsible for this increase as well as its occurrence in several members of the same family and in twins. Variations in diet may also explain the seasonal incidence and geographical distribution. The diet of the average American mother is normally very low in vitamin B, although she needs during pregnancy and lactation for the protection of her infant three or four times the amount of this factor that she does for her own well being. The authors in their laboratory by means of a deficiency of the vitamin B complex in the maternal diet produced pyloric obstruction in young rats. Other phases of the deficiency found in the same individuals or litter mates were hemorrhage and polyneuritis. In the animals thus affected the motor nerves to the pyloric region showed myelin degeneration, which is the typical pathology of a vitamin-B deficiency. This experimental work gives a basis for the prevailing theory that pylorospasm results from unbalance of the autonomic nervous system. Vitamin-B deficiency as produced experimentally and found clinically in beriberi occurs most commonly in males. In clinical pyloric stenosis from 75 to 90 per cent of the cases are found in boys, and this experimental series showed 87.5 per cent of males. Clinical experience bears out the experimental evidence of the association of pyloric obstruction with hypertonicity and hemorrhage. A subnormal temperature and cold extremities in premature or malnourished infants are often the first signs of a vitamin-B deficiency. As prophylactic for pyloric obstruction and other manifestations of a dietary deficient in the vitamin-B complex, every woman should receive desiccated yeast throughout pregnancy and lactation. The baby should also receive it from the beginning. After symptoms of pyloric obstruction have become manifest, treatment should include the usual atropin and thick cereal and also desiccated yeast. In serious cases blood transfusion is indicated.

## DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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UNIVERSITY OF PENNSYLVANIA.

**Untoward Reactions following Toxin Treatment for Dermatitis Venenata.**—TEMPLETON (*Arch. Derm. and Syph.*, 1929, 20, 83) reports five illustrative cases of an hitherto undescribed reaction to the administration of specific rhus antigen for poison oak dermatitis. The reaction may be either a localized urticaria at the site of injection of the extract or a generalized eruption may appear, composed of urticarial wheals and papulovesicles of dermatitis venenata. The pruritus is severe and hospitalization is frequently necessary. Either reaction may begin from twenty-four to seventy-two hours after the injection. The patient may or may not have had an allergic history. The writer believes that the patient is sensitized to the extract of poison oak by the disease itself, and that the patient reacts allergically to the injection of the specific antigen employed. To prevent these reactions, the writer has used gradual desensitizing measures by the use of small initial doses. Since the abandonment of the orthodox larger doses no further untoward reactions have been noted and the therapeutic results have been equally satisfactory.

**Bismuth is Absorbed.**—BOYD (*J. Am. Med. Assn.*, 1929, 93, 269) using potassium bismuth tartrate in oil believes the drug is absorbed satisfactorily intramuscularly, provided the dose is decreased and the interval shortened, that is, a dose of 0.1 gm. every three to five days, and that a scrupulous technique is employed, changing to a water-filled needle after the drug has been aspirated into the syringe. The injection is given slowly. Massage is extremely important, both immediately following the injection and with frequent massage at intervals throughout the course of the injections. Roentgenograms are used to check the absorption of bismuth. Eleven illustrative cases are reported.

**The Chlorid Content of the Whole Blood in Eczema.**—BURGESS (*Arch. Derm. and Syph.*, 1929, 20, 69) reviews the literature on whole blood chlorid studies and quotes Myers' normal figures as ranging from 450 to 500 mg. of sodium chlorid per 100 cc. of whole blood with lower figures as still within normal limits. The author did chlorid determinations on 5 normal individuals, obtaining a range from 429 to 462 mg. In a group of various dermatoses (acne, pemphigus and generalized pruritus) the determinations ranged from 413 to 492 mg.



In a series of 20 cases eczema (various types and clinical varieties) the chlorid range was from 426 to 495 mg. All of these results were in normal limits and high or low values could not be correlated with any clinical classification of eczema. The author points out that his findings demonstrate no abnormality in chlorid metabolism in eczema or other dermatoses investigated and that there is no rationale for attempting to reduce the chlorid content of the tissues by a salt-free diet or aiding chlorid elimination. Any satisfactory results obtained by the intravenous administration of sodium thiosulphate in eczema appears to depend on factors other than the alteration of the blood chlorids.

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**Incidence of Foot Ringworm among College Students.**—LEGGE, BONAR and TEMPLETON (*J. Am. Med. Assn.*, 1929, 93, 170) have made a survey on the incidence of ringworm of the feet in college students. They found the incidence in new men students to be 53.3 per cent and 15.3 per cent in women students. At the end of a year of physical education and gymnasium work they found the rate in men students raised to 78.6 per cent, while the women showed but a slight increase, that is, to 17.3 per cent. The observers believe the discrepancy in the increase of incidence between the men and women students (25.3 per cent as against 2 per cent) to be accounted for by the superior sanitary conditions obtaining in the new women's gymnasium. They point out that in addition the women would acquire less ringworm of the feet due to cleaner habits, a higher type of hygiene and lighter footwear. Emphasis is laid on the precaution of always wearing some sort of foot covering in the gymnasium, swimming pool runways and showers.

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## GYNECOLOGY AND OBSTETRICS

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UNDER THE CHARGE OF

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**Intestinal Obstruction following Baldy-Webster Operation.**—For many years one of the theoretical objections to the Gilliam type of operation for the correction of retroversion of the uterus has been the possibility of the occurrence of a subsequent intestinal obstruction due to a loop of small bowel being caught in one of the open spaces between the round ligaments and the abdominal wall. Such a possibility has seldom been considered following the Baldy-Webster operation, but the case reported by PEMBERTON and SAGER (*Surg. Clin. North America*,

February, 1929, p. 203) demonstrates that it can happen. In this case, in less than four weeks after a Baldy-Webster operation had been performed an acute intestinal obstruction developed, due to a loop of small bowel herniating from behind forward through the opening in the broad ligament through which the round ligament had been pulled in order to attach it to the posterior surface of the uterus. In another case which they report, although no obstruction developed, it was noted that as the result of a Baldy-Webster operation having been performed some twelve years previously there was an opening in each broad ligament at the site of the round ligament perforation large enough to admit two fingers which were certainly sites of potential internal intestinal strangulation. In order to prevent the occurrence of such a condition, they call attention to a point which Webster described in his original description of the operation and caution that it should always be observed, namely, that each round ligament should be stitched to the edges of the opening in the broad ligament through which it is pulled. This little point in the technique is probably frequently omitted, but its observance will most likely preclude the subsequent stretching of these small openings with the accompanying possibility of a life-threatening acute intestinal obstruction.

**Primary Epithelioma of the Vulva.**—A series of 71 cases of primary epithelioma of the vulva observed at the Mayo Clinic between 1907 and 1927 has been reported by RENTSCHLER (*Ann. Surg.*, 1929, 89, 709), who states that it is a rare disease, being 25 times less frequent than carcinoma of the cervix. Pruritus must be considered as a significant etiologic factor since 40 per cent of the patients gave a definite history of preëxisting pruritus. The most common symptom is itching. Ulceration may appear any time during the course of the disease and 47.5 per cent of the patients had ulceration when first examined. This is associated with pain, more or less discharge and at times with slight bleeding, then follows insomnia, secondary anemia, cachexia and not infrequently urinary complaints. A biopsy will differentiate the condition from metastatic growths, tuberculosis and syphilis when there is doubt as to the diagnosis. The local lesion may be of the superficial vegetative type or it may be of the deep infiltrative type. Metastasis may occur at any time during the course of the disease. The lymphatic drainage, with the exception of that of the clitoris, is first to the inguinal lymph nodes, usually on the same side, but drainage to the opposite side is anatomically possible and not infrequent. The lymphatic drainage from the clitoris is usually directed into the pelvis; similarly the inguinal lymph nodes drain directly into the pelvis. The regional lymph nodes may be palpable without containing malignant cells and conversely the nodes may contain malignant cells without being palpable. Therefore, the only way to be sure whether or not they contain malignant cells is to remove them and to study them histologically. Wide excision of the local growth and excision of the superficial and deep inguinal nodes on both sides, whether enlarged or not supplemented by radium and Roentgen ray treatment is the treatment of choice unless metastasis obviously has advanced beyond the point where surgical intervention can help the patient or unless the existing growth is of the third or fourth grade of malignancy, according to Broders' classification.

In these cases of grave malignancy it would seem wiser to excise only the local growth and supplement this by radium and Roentgen rays applied over the site of the original growth and the lymphatic drainage. In those cases in which there is obvious lymphatic involvement and a grave malignancy, radium and Roentgen rays alone should constitute the treatment because in these cases the recurrence is too prompt to warrant surgical procedures. Forty-five of the patients in this series are dead, all except one dying from carcinoma. The remaining 17 patients who are still living include 13 who are free from recurrence after an average duration of 7.77 years. One patient had a recurrence after eight years, 1 after four years and 1 within less than a year after operation. Therefore, the prognosis is fair for prolongation of life but poor for cure and would seem to be in direct proportion to the grade of malignancy.

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF

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**The Use of Ultraviolet Rays in Diseases of the Nose and Throat.**—The biologic action of light is due primarily to photochemical reaction. Waves of light are absorbed by living cells and produce photobiochemical reactions which influence the whole organism. All living cells are sensitive to the ultraviolet rays from 3100 to 2500 Angström units, which penetrate to the superficial layers of the living epidermal cells, producing at the site of irradiation an erythema characterized by hyperemia, leukocytic infiltration and an intradermal edema due to transudation of fluids and exudation of plasma. On the theory that at the site of irradiation there is produced a bactericidal substance which is distributed throughout the body by the circulatory system, EIDINOW (*J. Laryngol. and Otol.*, 1929, 44, 177) has adopted a special technique of general treatment, using a quartz mercury-vapor lamp which emits ultraviolet rays shorter than 2970 Angström units. Irradiation of approximately one-sixth of the body surface is conducted two to three times a week, but an interval of from ten to fourteen days is allowed between exposures of any given cutaneous area. He reports that "early cases of lupus of the skin, nasopharynx, palate and larynx have been healed by these means." Eidinow states that a direct bactericidal action from ultraviolet irradiation is an erroneous impression, inasmuch as serum and lymph greatly impede the penetration of the bactericidal rays, while excessive dosage produces extensive edema and necrosis. Careful dosage in local treatment, however, hastens the repair of many types of septic wounds. As the normal mucous membrane is about three times as sensitive as normal white skin to light, the dosage must be regulated with great care. He believes that the use of quartz rods, applicators and mirrors to transmit or reflect the light to the site of

infection is unsatisfactory, due to the reduction in intensity of radiation. The author concludes by mentioning that further research on treatment by means of sensitizers and ultraviolet radiations emitted by high-frequency current are in progress.

**Irradiation from Quartz Mercury-vapor Lamp as Factor in Control of Common Colds.**—By exposing a group of individuals, who were susceptible to the "common cold," to the irradiations of an ordinary quartz mercury-vapor lamp once a week for a period of from ten to eighteen minutes (dividing the time of exposure equally to the front and back of the naked body) at a distance of 30 inches, MAUGHAN and SMILEY (*Am. J. Hygiene*, 1929, 9, 466) found that as a rule the incidence of colds was reduced by at least 40 per cent. The treatment was carried out during the dark months of the year, when fewer solar ultraviolet rays are available. Inasmuch as the absence of ultraviolet radiation constitutes only one of several recognized factors capable of reducing general resistance to acute respiratory infection, it is not to be expected that the supplying of this deficiency will prevent the occurrence of all cases of "common colds." However, the authors believe that their results indicate a justification for the employment of ultraviolet therapy at weekly intervals in those persons showing a marked tendency to recurrent head colds.

## RADIOLOGY

UNDER THE CHARGE OF

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**Natural Heliotherapy.**—Present day theory, says GOTTLIEB (*Arch. Physical Therapy, Roentgen Ray, Radium*, 1929, 10, 110), recognizes that every chemical reaction is started by radiant energy. The living animal absorbs stored up sun energy in the form of food, which, in itself or in its original form, the sun ray, excites the living organism to activity accompanied by setting free stored up energy. This latter is expressed in greater viability, body and mental activity. Whenever body energy is deficient, heliotherapy finds its indications. The value of sun radiation has been proved in rickets, osteomalacia and delayed union of fractures. It is beneficial in localized wounds, ulcerations due to circulatory or neurotrophic disturbances, and infected wounds. Chronic osteomyelitis, chronic arthritis and syphilis refractory to treatment are favorably influenced. Besides tuberculous bone and joint affections, heliotherapy is indicated in deficiency diseases of the

type of Osgood-Schlatter, Legg-Perthe, Freiberg, Koehler and other conditions classed as osteochondritis.

Proper effects are obtained only by proper dosage. Overstimulation is likely to occur unless the treatment is individualized and supervised. It should be commenced with air baths daily for five minutes, increasing the time until tolerance for the temperature of the air is created. Only then should the sun rays be introduced, beginning with small doses and slowly increasing to the maximum of tolerance, which varies considerably.

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**Colonic Diverticula.**—CASE (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 207) observes that diverticulosis of the colon is a symptomless condition commonly met with at roentgenologic examination. Diverticulitis, which is an inflammatory reaction to diverticulosis, is also commonly encountered, the inflammatory sequels manifesting themselves in various ways so that cases may be clinically classified as of the enterospasm type, the hyperplastic type and the pseudo-appendicitis type. When enterospasm predominates there are the ordinary signs of chronic colitis with no indications of tumor or obstruction. In this type a sudden development of acute symptoms may suggest a left-sided appendicitis. In the hyperplastic, obstructive type the symptoms are those of long standing constipation, colicky pains and usually a palpable tumor. For the roentgenologic examination Case feels that both the opaque meal and enema are necessary. The roentgenologic differential diagnosis involves sigmoiditis, hyperplastic tuberculosis, actinomycosis, syphilis, and, most especially, carcinoma. No case of supposed carcinoma of the lower bowel should be regarded as inoperable either before or during laparotomy until the question of diverticulitis has been considered and if possible settled.

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**Iodized Oil and Pneumoperitoneum in Roentgen Gynecologic Diagnosis.**—As a result of increased experience, STEIN and ARENS (*Radiology*, 1929, 12, 341) have become more cautious in the diagnosis of tubal obstruction, and consider spasm to be a definite and frequent phenomenon in normal pelvic viscera. They feel that spasm as exhibited in the uterus and tubal isthmus is comparable to spasm observed in other hollow viscera, and is a defense reaction against the introduction of a foreign substance or against distention. This phenomenon accounts readily for the numerous cases in which they found apparent obstruction, in which gas alone was used for testing tubal patency, and in which on repeated tests the tubes proved to be patent. This was graphically illustrated when iodized oil was utilized showing one or both tubes patent immediately following the usual patency test with gas in which the tubes appeared to be obstructed. The converse has also been observed, namely, that after a satisfactory patency test with gas the instillation of iodized oil yielded a typical picture of cornual or isthmic obstruction. Again, one tube has appeared filled and the other empty. The experience of the authors emphasizes the necessity for repeated patency tests when obstruction is encountered, especially in the absence of obvious inflammatory lesions.

**NEUROLOGY AND PSYCHIATRY**

UNDER THE CHARGE OF

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**Mental Hygiene and the Practice of Medicine.**—STRECKER (*Mental Hygiene*, 1929, 13, 343) believes that psychiatry has much to offer the general practitioner. He considers that in every person who is sick there is an unknown factor representing his peculiar reaction as an individual. Since psychiatry has methods to impart that make it possible and feasible to recognize and handle this factor, it would be valuable to anyone treating patients. The objections to psychiatry, he believes to be founded on misconceptions. While it is necessary and desirable to place mental patients in special hospitals, this is also true of almost all of the specialties. The objection that treatment of mental patients is individualized and can have no application in other fields he holds to be erroneous on the grounds that it has a wide range of usefulness. The adoption of hydrotherapy, occupational therapy, and so forth, in general medical practice, he gives as examples of such application. Statements that the etiology is unknown in psychiatry he meets by showing that in many instances the etiology is quite definitely known and that in the obscure instances the psychiatrist is no worse off than are those who treat cancer, and so forth. As to legal entanglements he contends that these are no more prevalent in psychiatry than they are in other specialties. On the other hand, he believes that any failure to take psychiatric conceptions into the field of medicine impairs the efficiency of the physician. The occurrence of mental symptoms in relation to typhoid fever, encephalitis, goiter, and so forth, make some understanding of psychiatry and psychiatric therapy essential. The mere handling of a patient prior to an operation, he believes, may make the difference between a successful and an unsuccessful procedure. During convalescence from any serious illness he believes the problem to be primarily psychiatric in nature and that many cases, if handled properly, can be prevented from arising too soon and thereby causing a relapse, or from falling so deeply in love with their illness that they remain chronic invalids. During the acute life periods again psychiatry is invaluable. Since 70 per cent of the daily contacts of physicians are made up of functional and not organic pathology, the author believes that the physician should handle functional disease in all of its aspects, only resorting to the specialist for cases which are beyond his scope. He gives a general plan of treatment in these cases.

## PATHOLOGY AND BACTERIOLOGY

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UNDER THE CHARGE OF

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**Tuberculous Cervical Adenitis.**—MILLER and SHEDDEN (*Am. Rev. Tuberc.*, 1929, 19, 511) discuss the present status of the problem of tuberculous cervical adenitis and indicate that the localization of this infection does not constitute an individual disease, but that it is probably associated with foci elsewhere. They tend to agree with Krause that tuberculosis is a constitutional or diffuse infection resembling syphilis, with numerous loci, but with few manifest foci of anatomic change. The authors have studied a series of cases of tuberculous cervical adenitis, and find that in the early stages of its existence free tubercle bacilli may be disseminated, resulting in a mild bacteremia. Thus distant as well as local tuberculous processes are developed. The condition lends itself to general treatment, and surgery is to be considered only when other measures have failed.

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**Skin Hypersensitiveness in Rheumatic Fever.**—The problem of the cause of rheumatic fever is far from being settled. It has been suggested that the disease is an allergic phenomenon and many attempts have been made to discover a specific allergin. BIRKHAUG (*J. Infect. Dis.*, 1929, 44, 363) in a report on skin tests performed in European clinics with filtrates, autolysates and bacterial suspensions of nonmethemoglobin-forming streptococcus, *Streptococcus viridans* and hemolytic streptococcus, considered that a nonspecific, common allergenic factor is present excessively in the bacterial products of indifferent and viridans streptococci and moderately present in the solutions of hemolytic streptococci, to which, cases with either acute rheumatic infections or chronic infectious arthritides, react hyperergically. Since tuberculosis is the typical example of allergy it is of interest that REITTER (*Wien. klin. Wchnschr.*, 1928, 41, 473) found four-fifths of persons with acute articular rheumatism to give distinct allergic reactions after intracutaneous tuberculin and he hypothesized that it is only in such hypersensitive persons the symptom complex of acute articular rheumatism develops. WILKINSON (*Brit. Med. J.*, 1928, i, 749) also believed that the symptom complex hitherto associated with "rheumatism" may be the effect of tuberculosis and advocated the use of tuberculin in detecting the variety of lesions which occur in the early stages of chronic tuberculosis. Thus it is seen that the ill-defined symptoms under the term "rheumatism" are still open to different interpretations and the ideas on the subject are still in a state of flux.

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**Immunologic Studies of Typhoid Vaccination by Mouth: I. Agglutinins Formed in Persons Treated Orally with Triple Typhoid Bacterin.**  
—A new interest in the phenomena of local immunity has been stimulated by the recent work of Besredka. The evidence for oral immunization against the typhoidal fevers has largely been based on clinical data. To determine a possible experimental foundation for such clinical claims, HOFFSTADT and THOMPSON (*Am. J. Hyg.*, 1929, 9, 1) undertook the present study. Of the 134 persons treated orally with the triple typhoid bacterin (98 with the liquid bacterin and 36 with the typhoid capsule), 87.7 per cent gave positive agglutinins for typhoids. Of the 74 persons who were tested for complement fixations, 83.5 per cent gave positive reactions. This agrees with the results reported for the subcutaneously inoculated individuals. A slightly higher percentage of the group treated with liquid bacterin gave positive reactions than the capsule-treated individuals. The percentages positive of the bile-treated persons were higher than those not treated with bile. In the bile-prepared group which was treated with liquid bacterin the titers for agglutinins were higher than in any other group. The bile was given in those cases before the administration of the bacterin. It appears, therefore, that it may be better to separate the bile from the bacterin and give it before the first dose rather than simultaneously with all three doses of the bacterin. From these results the authors conclude that agglutinins, and complement fixations can be produced by oral inoculation of individuals with triple typhoid bacterin in the dry form as a capsule. There is no delay in the appearance of the agglutinations or complement-fixation reactions over that which was found in the liquid triple bacterin method. Neither antibody is consistently present in the immune person.

**The Transfer of Tuberculosis by Dust and Other Agents.**—AUGUSTINE (*J. Prev. Med.*, 1929, 3, 121) made tests to determine the presence of tubercle bacilli: (1) In the air in the rooms of tuberculous persons; (2) in the dust upon surfaces in their rooms; (3) in the dust removable from their clothing; (4) in the washings from the hands of children living in their homes. The experiments were made in the houses of families of which one or more members had tuberculosis with sputum positive for tubercle bacilli. The evidence collected suggests that



the demonstration of virulent tubercle bacilli in dust collected from the rooms or clothing of patients with open tuberculosis may be used as a measure of the danger to which those in contact with the patient are subjected. Dust from the rooms or clothing of patients who keep themselves clean contain tubercle bacilli much less frequently than dust from uncleanly homes and people. Tubercle bacilli are recovered more frequently from the rooms of women than of men with open tuberculosis, and less frequently from the clothing of women than of men. These relations may be explained by the greater personal cleanliness of women and their inability, when ill, to keep their houses clean. Tubercle bacilli are recovered more frequently from the homes and clothing of colored than of white patients. The number of tubercle bacilli in the sputum of the patient is a factor in determining the presence or absence of tubercle bacilli in surrounding dust. The author's data cannot be used to determine the relation of infected dust to human infection because most of the families studied had long been exposed to open tuberculosis. To determine whether tubercle bacilli in the dust of houses infect members of the household it would be necessary to continue observations similar to those reported over a period of years in order to discover the frequency with which latent and manifest tuberculosis make their appearance in those who have been exposed to infected dust.

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**Detoxifying, Diffusing, Germicidal and Surface Tension Depressing Properties of Soaps.**—DAVISON (*J. Infect. Dis.*, 1928, 43, 292) prepared twelve common soaps and studied their detoxifying, diffusing, germicidal and surface tension depressing properties. He states that soaps possessing high detoxifying ability diffuse readily, are highly germicidal, but are correspondingly ineffective surface tension depressants.

**Correction.**—On page 437 of the September issue, the reference to Yates' article should be to the *J. Laryngol. and Otol.*, 1928, 43, 852, and not to the *Arch. Otolaryngol.*, as would be inferred.

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ORIGINAL ARTICLES.

ARTHRITIS.\*

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THE opportunity of speaking upon the subject of arthritis is welcomed because the invitation to do so carries with it evidence of the awakening appreciation on the part of the profession for the great problem involved. Arthritis and rheumatoid disabilities constitute the oldest disease entity of which there is any record, as is amply illustrated in the fossilized remains of the reptiles of the cretaceous period, long antedating the advent of man. Men of the Old Stone Age suffered from arthritis, and it was, as one writer put it, the disease par excellence of the Egyptians. It was a cause of so much disability to the Greeks and Romans as to account for the establishment of such natural spas as Aix Les Bains in France, which has had a continuous existence of two thousand years. Notwithstanding this, and the importance of the disease as one of the great problems of medicine, arthritis has received less intensive and concerted attention than have many disturbances of lesser import.

Owing partly to the refractory nature of the disease itself and partly, perhaps, to a sort of obloquy reflected from certain irregular cults of treatment, a curious inertia seems to have characterized the attitude of the profession as a whole toward arthritis for many decades. Interest and investigation in this great field have definitely not kept pace with the advance of medicine as a whole.

\* Mary Scott Newbold Lecture (delivered at the College of Physicians, Philadelphia, November 7, 1928).

Horace says in one of his odes "Rusticus expectat dum defluit amnis" ("the rustic waits for the stream to run by"); and one might conclude that the profession has alike waited for the constant stream of arthritics to dry up.

Fortunately, a sharp awakening from this attitude of indifference has recently come about. A chief factor in this has been the establishment nearly everywhere of provisions for insuring the working classes. As has not infrequently happened in medicine, interest in the problem was brought about partly through the back door, so to speak, and the profession, especially in Europe, is now somewhat in the position of being goaded on by the demands of the "sick funds" organizations, that something be done to reduce their losses from arthritic and rheumatoid disability. It will come as a surprise to some to learn that in Berlin alone, the incidence of rheumatoid disability is 3.4 times greater than that due to tuberculosis. In England, one-sixth of the sum expended under National Insurance Acts was for diseases classed as rheumatic, and half of this was for chronic arthritis alone. In Sweden, four hospitals have been created for the exclusive care of chronic arthritics. In London, a very large clinic is being established under the auspices of the Red Cross for the purpose of extending the benefits of physiotherapy in a wide sense to sufferers from arthritis. Many other instances of the kind could be cited which show beyond doubt that for the first time in the history of medicine something approaching a concerted attack is being made upon this disease.

It is of much significance to note that within the last two years a committee for the study of arthritis has been established in this country, largely under the originating impetus of Dr. Louis B. Wilson, director of the Mayo Foundation, whose attention was called abroad to the importance of the problem. This committee consists of a dozen representative men chosen from geographical extremes of the United States and Canada and has held two meetings. Reference will be made to some of the steps planned and taken.

In general, the attitude of the profession in Europe toward arthritis has been marked by somewhat more catholicity, especially as regards etiology than has been the case here during the past ten years and the American committee has reached a somewhat comparable viewpoint. One of the first steps undertaken by it was an attempt at simplification of classification, long the bugbear of students of the subject. It has been decided to recognize two great types of arthritis, atrophic and hypertrophic. This is in fact, under other names, the classification into the proliferative and degenerative types of Nichols and Richardson. All types of arthritis, exclusive of tuberculous, are included under these heads. The outstanding pathologic deviations are, in the atrophic type, smothering and destruction of cartilage by overgrowth of the synovial mem-

brane, together with a destructive growth of granulation tissue from the bone below; and, in the hypertrophic type, fibrillary degeneration of cartilage together with overgrowth of bone at the margins of the joint and elsewhere. Manifestations of the same underlying processes occur in the soft tissues also, but fall, more particularly perhaps, under the head of the atrophic variety. It is important to note, as Charcot pointed out in his Salpêtrière lectures forty years ago, that arthritis and rheumatoid disability are only branches of a large pathologic tree which has its roots in disturbances of widespread underlying physiologic processes.

In a brief article such as this, however, there is no opportunity to present at length the many factors in etiology, pathology, or treatment which must be considered in any thorough review of the subject. It is rather the purpose of this paper to sound some of the newer significant notes in relation to the disease. In this connection an important conclusion of the American committee on arthritis must here be mentioned, which may come as something of a surprise to many who have accepted whole-heartedly the rather crystallized opinion in this country of the cause of arthritis. Recognition of the importance of focal infection in a host of diseases has marked a signal advance in modern therapy and reflects credit upon American medicine more than upon that of any other country. In no other disease has the importance of focal infection been more apparent than in the case of chronic arthritis, particularly in relation to the many varieties of streptococci. So much has this been the case, that, in many quarters, the rheumatoid problem has been regarded as one solely of bacteriologic nature. Suffice it to state then, that, in the views of many of the committee, focal infection or infection of any kind, though in no sense to be minimized, constitutes often only an episode in the causation of the disease, acting like "the match to the priming." Indeed, the committee has placed itself on record as believing that the underlying causes are often farther to seek and are to be found, in part at least, in that background determined by heredity, constitutional make-up, the equilibrium of the nervous system, chemical and other toxins of imponderable nature and, finally, the conditions of the environment. This may seem somewhat too inclusive a statement and yet it is only with full consideration of the lines here implied, in the opinion of many of the committee, that successful treatment of the disease can be carried out. One natural result of the brilliant development which bacteriology has undergone in the past five decades has been a somewhat mechanical view of the depredations of bacteria in their effects upon tissues. Wells points out, however, that practically all bacteriologic processes are at last analysis chemical in nature.

Thus, it is the view of Zinsser that rheumatic fever is an allergic condition in which the body is sensitized to a bacterial antigen. He believes this to be the only explanation consistent with the

varieties of bacteria isolated through the interesting work of Small, Swift, Clausen, and others and with the frequency with which such factors as exposure seem to precipitate the attack. Swift remarks that it is easy to understand that the state of the tissues of the patient is the most characteristic feature of the disease and that the specificity of the streptococci recovered, may play a relatively unimportant rôle. Recent evidence suggesting the passage of certain strains of streptococci from one to another is in line with this view.

It seems highly probable, by analogy, that the atrophic forms of chronic arthritis may often have a comparable cause. As long ago as 1920 the present writer<sup>1</sup> advanced the then somewhat iconoclastic view, based upon observations in the army, that acute inflammatory rheumatism and the exacerbations of chronic arthritis seem to differ in degree rather than in kind.

The toxicity of extracts of the organisms isolated by Small and by Birkhaug, to mention only one influence, is so marked as to lead to the hope that among arthritics as a whole, a group may be found which will stand in some specific relationship to these or comparable organisms.

In view of these several considerations, it would appear that even the bacteriologic causation of arthritis proceeds in many cases from a wider premise than has been generally appreciated. Zinsser<sup>2</sup> says, "It is our opinion that in that branch of general physiology which is spoken of as immunology, we have been hampered in our reasoning by adhering too closely to analogies furnished by a few antigenic substances such as bacteria, animal cells and coagulable proteins. We are actually dealing with phenomena of much broader physiological interest." It is pertinent, therefore, to quote one sentence from a little brochure or primer which has been prepared by the American Committee for the Control of Rheumatism for distribution to the laity and, indeed, somewhat to the profession also.

"The commonest causes of atrophic arthritis are the poisons which are set free in our bodies. These poisons may be manufactured by the growth of germs which the body's defense mechanisms are too weak to resist or by a disturbance of normal physiology and chemistry of the body which may result from overtire and the bad use of our bodies."

In this connection should be mentioned another of the acknowledgedly prime factors in the causation of arthritis, especially of the hypertrophic type, in women—the menopause. The relationship is so clear that some students, have described specifically "arthritis of the menopause." In the view of some observers including Knaggs, Cecil, Osgood and Goldthwaite, hypertrophic arthritis is not of infectious or bacteriologic origin. Space has been given to the several considerations so far mentioned, because it is believed that they con-

stitute a new "take-off" in the approach to arthritis, of significance, in treatment, to the many sufferers from this disease.

The present is not the time for consideration of statistics except to mention that arthritis as a whole affects women with about twice the frequency of men, that the knee is the site of greatest involvement in all groups, the fingers coming next, and that in a study based upon 1100 cases by Dr. Peirce and the writer,<sup>3</sup> heredity played a rôle of unsuspected importance, being obvious in 60 per cent.

Study of the morphologic changes in the arthritic syndrome has been exhaustive but study of the dynamic pathology causative of the changes has been in general meager. How are they brought about? It is impossible to investigate a disease in which rarefaction and overgrowth of bone are so conspicuous without being early impressed with the fact that it is necessary to invoke chemical reactions, in part at least, to explain the changes involving the calcium and magnesium of osseous tissue. Chemical analysis, however, of the fasting circulating blood along modern lines has been singularly unfruitful, although it has served to delimit the problem and direct attention into other channels. It may be said, however, that in arthritis as a whole, basal metabolism tends to be low; according to Swaim and Spear, chiefly in the degenerative type. It may be mentioned also that there is no apparent disturbance of the nitrogenous metabolism *per se*, and that there is no justification for withholding red meat from the arthritic as so long, and still so widely and erroneously, advocated. The frequency of anemia in arthritis and the importance of organs and other tissue for blood regeneration make this a matter of large importance.

It is only when one turns to a study of the arthritic by imposing on him a physiologic load of some sort, that one detects inadequacy of response, indicative of pathologic deviation.

One line of evidence, adduced in this way, came as the result of observing that certain low dietaries were of benefit to certain types of arthritis. In the attempt to throw light upon this through laboratory studies, it was ascertained that in the arthritic certain substances are removed from the blood, after ingestion by mouth, more slowly than is the case in health. In brief, 76 per cent of arthritics show actually or potentially a delay in the removal of dextrose from the blood and in this same blood there is also a higher percentage saturation of oxygen than normally occurs. Attempts to explain this phenomenon upon chemical grounds were unsuccessful and recourse was had to the hypothesis that the process was mechanical in nature, depending upon changes in the blood flow. Experiments were accordingly devised in which the circulation was cut off in three limbs, with the result that, upon feeding dextrose, it was possible to induce precisely the same phenomenon as occurs in the majority of arthritics. It thus appeared that the explanation

of the dextrose and oxygen values was referable to the failure of the blood to reach at least some tissues in which the removal of these substances normally quickly occurs. The cause of this interference with the circulation was conceivably to be found along the line of vasoconstriction. Attempts were accordingly made to ascertain whether the peripheral blood gave any evidence of this in terms of the blood count or other changes in the corpuscular elements.

In a series of careful studies, Dr. E. G. Peirce has shown that there tends to be a difference in the blood first issuing from peripheral capillary beds in the arthritic as compared with normal persons. This difference consists in a lower red-cell count in the first issuing drop as compared with later drops. In the normal, an opposite state of affairs obtains and the count of the first drop is higher than that of subsequent drops. This can be interpreted to mean that there are fewer cells in the peripheral vascular spaces of arthritics or that these spaces contain unduly large amounts of fluid. That these observations are not the result of chance or technical error is well illustrated by the fact that this low cell count in arthritis can be restored to normal by many of the measures which are of value clinically to the arthritic. Thus, exercise, the salicylates, coffee, external heat and massage induce a marked return toward the normal picture.

It then became desirable to check this further, if possible, by determining the actual state of the capillaries themselves and this was made possible by the method of direct inspection devised by Lombard fifty years ago and left buried until recently in the literature. A long series of studies was conducted upon normals and arthritics by Dr. Peirce, Dr. F. A. Cajori and the writer<sup>3</sup> as the result of which it has become reasonably clear that there is in arthritis a condition of the capillaries characterized essentially by a slow and interrupted bloodflow; constricted or, at all events, many empty vessels; and especially a generally "anemic" condition of the peripheral tissues studied. It has been possible fortunately to check this further by means of measures and drugs which benefit the arthritic and it was again found that following such measures as massage, exercise and aspirin the whole picture changes to one of adequate bloodflow, only to relapse again, however, upon cessation of therapy.

Dispassionate consideration of these several observations afforded striking evidence that at least part of the pathologic deviation productive of the symptoms and morphologic changes of arthritis is to be found in the altered state of the bloodflow in the finer vessels, probably in the nature of vasoconstriction. This is precisely in keeping with the clinical observation of the frequency with which Raynaud's syndrome is encountered in the rheumatoid state. It also fits in well with the long recognized clinical effect upon blood-

flow of the measures probably most used in arthritis, such as heat, massage, etc. It remained, however, for further experiment to place the matter upon a more secure footing. This experiment consisted in the attempt to interfere in the living animal with the circulation in the neighborhood of a joint. For this purpose, the writer's associate, Dr. A. D. Goldhaft, conducted a series of experiments in which the circulation to the patella was cut off by means of a purse-string suture carried around it. Six dogs were operated upon, using the other legs as controls. It was of the greatest interest to observe after some weeks, under the Roentgen rays, evidence of overgrowth of bone such as is seen in the patella of human beings suffering from hypertrophic arthritis of the knee. This result was forthcoming in every animal operated upon. That it was not due to the mechanical irritation of the operation, or of the silk ligature used, was shown by the fact that an equal amount of ligature placed near the patella without interfering with the blood supply, produced no change of organic or even functional nature. This experiment, then, coming as it did at the end of a series of observations all pointing the same way, is in agreement with the work of Wollenberg, and strongly suggests that the functional and organic changes of at least some kinds of arthritis, namely, the hypertrophic, are referable, in part at least, to a disturbance of the circulation. There is no opportunity here to point out the consequences which could be expected to follow anoxemia, not to say a relative anemia, of this kind but disturbance of the acid-base equilibrium is generally recognized to be one of them and the way is opened up for explanation of some of the changes, such as rarefaction and overgrowth of bone, in which the fixed bases of the bone must necessarily take part. The tendency towards a lowered basal metabolism in arthritis is probably to be explained on the same basis, *viz.*, a curtailment of the finer bloodflow in at least the muscular tissues.

Another line of observation which must be briefly mentioned as of significance in the attempt to understand the mechanism of arthritis is to be found in the observation by Cajori and the writer that certain substances which reach the gastrointestinal tract through the mouth are carried directly, after absorption by the blood stream, to the joints themselves and can be redetected there almost immediately in the synovial fluid. Indeed, certain substances, presumably crystalloids, such as glucose, reach a higher concentration in the synovial fluid than may occur in the blood, possibly because the arterial blood supply to the joint exceeds the venous outgo. This observation affords definite evidence of a means of nourishment of the central avascular area of articular cartilage, a matter long in doubt. It also unmistakably proves that a variety of substances from the intestinal tract has access to the joint cavities. The possibility that deleterious as well as nutritive substances



from the bowel may here play a rôle must henceforth be definitely considered. It may be noted in passing that Freiberg has recently shown that sterile bacterial filtrates injected into the joint cavity of animals may produce changes characteristic of atrophic arthritis.

**Treatment.** It is axiomatic that study of the problem of arthritis has for its aim amelioration and prevention of the disease. A consideration of the rheumatoid problem from the viewpoint of such physiologic changes as are above described offers explanation of the rationale of many measures of value and suggests in an important way certain lines which treatment must follow. We do not know all that should and must be known about the disease but there can be no doubt that information at our command today enables us definitely to take a more hopefully constructive attitude than at any time in the past. As with many other diseases, treatment must take the direction of removing possible causes, removing or modifying the functional and organic changes which the disease produces, and finally, when necessary, adjusting the burden which a handicapped organism is asked to bear.

In the first connection, the question of focal infection comes prominently into the foreground but I take it that with the present audience there is small need to stress the recognized rôle which infectious processes may play. This rôle must have full emphasis in any consideration of treatment. That infectious processes do not constitute the whole picture, however, has already been stressed and is further evidenced by the fact that in 400 cases of arthritis among soldiers during the war, three times as many recovered in the presence of causative focal infection as got well following its removal. The sound position to take, of course, is to spare the subject all burdens of this nature compatible with good medical and surgical judgment after thorough and dispassionate analysis of the case. The duty of the practitioner, however, has only begun in most cases when abscessed teeth are removed or a boggy prostate is massaged.

There remains in chronic arthritis, following the removal of even causative infections, a more or less chronic dislocation of physiology which may persist a long time or even permanently. So much is this the case that one may almost say, once an arthritic, always potentially an arthritic. It was remarked earlier that constitutional and environmental circumstances play an important rôle in determining arthritis and there is today small doubt that the nervous system is importantly caught up in the production of the disease. This is amply illustrated in the most extravagant expressions which arthritis takes, namely, the grotesque bony overgrowths of Charcot's joint. Specific evidence to the same end is also seen in the experiments of Adson and Rowntree, who were able to relieve, at least temporarily in 2 cases, all symptoms of severe atrophic arthritis of the legs by

the operation of lumbar sympathectomy. The frequency with which arthritis implants itself upon individuals of asthenic and enteroptotic build, forces upon the critical student of the subject the necessity of correcting the background if permanent results are to be achieved. In this connection one of the most useful lessons ever adduced has come from the Boston orthopedists who have developed a viewpoint of much wider value than the term orthopedic implies. This has to do with the rehabilitation of the deranged physiology in the chronic arthritic or the structurally inferior subject. The lesson is one which every internist should be able to apply to the neurasthenics and, indeed, many cardiac and other types of patients under his care. Speaking as an internist, the writer believes that internal medicine has, perhaps, regarded illness too often from the standpoint of the organs concerned and too little from the standpoint of the structure in which they are housed. As regards arthritis, the writer is strongly of the opinion that no one is qualified to approach this great problem who is not familiar with these measures of structural rehabilitation of the chronic invalid at large. In fully one-third of all arthritics this constitutes a foundation without which no substantial superstructure can be expected to rise.

In view of what has been said regarding the necessity of obtaining or maintaining a physiologic balance, it does not surprise us to learn that one of the most important measures to be instituted early in the treatment of the disease is rest. By this is meant systemic rest of the body as a whole and not necessarily rest of the affected part which is determined by other and local considerations. As regards the joints themselves, it is the belief of some of the most qualified observers that, in general, rest of the joint in atrophic arthritis is not desirable, whereas in hypertrophic arthritis rest of the joint affords removal of one of the causative etiologic factors. Many cases of arthritis originate in fatigue. Many more suffer fatigue from fighting the disease and from carrying on with the fox at their vitals. Fatigue is also an expression of toxicity and unless the sufferer be given a chance to recover from the lesser disability he will be quite unable to fight the greater.

Apart from the significance of rest as a specific measure, it has another importance in relation to various other forms of treatment, especially physiotherapy. Rest must be used in extra dosage, so to speak, when demands are being made upon the organism to respond to various therapeutic procedures, nearly all of which exact their toll of fatigue.

Perhaps the oldest, and certainly one of the most important categories into which treatment of the arthritic must fall is that of physiotherapy. Under the two great heads of massage and heat, sufferers from arthritis have in an untutored way themselves sought

relief through these measures over periods of centuries. The value of massage, exercise and heat to internal medicine at large is just beginning to be appreciated by the profession as a whole. The recent creation of the Council on Physical Therapy of the American Medical Association can be instanced in evidence of this, and it is said to have been one of the regrets of Dr. Weir Mitchell, whose name is so closely associated with this hall in which we are meeting, that his efforts at extending the use of physiotherapy fell so far short of the aims he had in view.

Orthopedic surgeons and neurologists, almost alone among medical men, appreciate fully the value of massage and heat. The proper prescription of these agents is almost a specialty in itself and it can only be added here that these measures serve the several purposes of relieving much suffering, restoring deranged physiology and modifying organic disturbances of structure.

Mention must be made of vaccine therapy and the use of non-specific protein. The use of these measures springs directly from the bacterial origin of many cases of arthritis and needs no defense or emphasis in the treatment of infections. Their place in arthritis is established in relation to one exciting factor of the disease, but those who best understand the principles of operation best understand also the limits within which they should be employed.

The most hopeful sign in this connection proceeds from the allergic conception of the etiology of many cases of the atrophic type and it is to be hoped that the organisms isolated by Small, together with that of Birkhaug and, more recently, Cecil, may prove to be utilizable in the direction of desensitization or increased immunity.

Nonspecific protein therapy has its origin in somewhat comparable premises and is so widely accepted, even in the treatment of paresis by malaria, as to need no particular mention. Its value in arthritis, in a limited but definite number of cases, may depend in part upon certain antigenic or other specific properties, but it is also certain that part of the benefit is referable to the heightened metabolism induced. Instances are legion in which the symptoms of arthritis have disappeared entirely in the presence of hyperpyrexia from pneumonia or typhoid, with the increased metabolism and accelerated blood-flow which they inevitably bring about.

Vaccines and nonspecific protein should be used with a balanced appreciation of the nature of the disturbance and what they may be expected to accomplish. The limits and dangers of physiotherapy constitute part of the lesson to be learned in relation to that field; and by the same token, the limits and dangers of vaccine therapy are also to be kept in the foreground.

Co-equal in importance with the bacteriologic factors in arthritis, in the usual sense of the word, and possibly surpassing them, both

etiologically and therapeutically, is the great field constituted by the gastrointestinal tract. Apart from the question of local foci, such as an infected gall bladder or ulcerative colitis, the intestinal tract plays unquestionably a large rôle dependent upon the still unmapped processes of fragmentation of the foodstuffs and the formation of the products of normal bacteriologic activity. Ten years ago this conception had little acceptance; today, it is so widely appreciated that the laity are flocking with their well-known vogue for "cures" to the many establishments given over to colonic irrigation, facetiously referred to sometimes as "colon filling stations." As is usually the case with new ideas in medicine, enthusiasm for this procedure runs ahead of the facts and yet there can be no question that through this type of agency we have a means of removing or modifying one of the great causative factors of arthritis. The rationale of this measure is too complicated for detailed mention here but probably depends in part upon removal of the products of bacteriologic growth. That this is not the whole explanation, however, is pretty clear from the fact that change of the intestinal flora does not necessarily have any beneficial influence. Faulty anatomy and faulty physiology of the viscera and especially of the intestinal tract apparently afford the basis upon which the exciting factors can become operative.

If there be value in expediting out of the gastrointestinal canal its complicated and varied contents, it should and does follow that control of the intake of the substances thus sought to be expedited, should also be important. It is precisely that taken in by mouth which, in large part, is removed by irrigation. Beyond question, a large field of therapy here presents, the high points of which only can be outlined. The form which it takes is chiefly in the direction of a lowered caloric intake at large, though there is reason to believe that the starches and sweets are more deleterious than the other foodstuffs. The operation of a low dietary is probably dependent partly upon removal of the substrate on which the intestinal flora subsist but also upon an indirect metabolic influence, which cannot be developed here because of limitations of time. One of the basal facts relating to arthritis is caught up in the influence of a heightened bloodflow and increased metabolism upon the disease. By the same token, it is precisely when catabolism runs ahead of anabolism that the arthritic may experience temporarily some of the sharpest benefit. When a restricted dietary brings about this state of affairs, certain cell units are apparently not only spared a previous burden but they function with a reserve potential which, while the situation lasts, constitutes physiologic equilibrium. The dangers of undernutrition, however, present limiting factors in this type of therapy and it can be practised only with a balanced appreciation of both sides of the equation. When it happens, in suitable

sthenic cases, that a reduced dietary can be accompanied by the use of physiotherapy, not only is the physiologic load lightened but at the same time a metabolic fillip is also given to the flagging horse. The late Cardinal Gibbons is said to have remarked that he owed his good health to his bad digestion. Perhaps to few other types of invalids has this epigram such application in principle as to the chronic arthritic. If there were more dyspeptics, so to speak, there might be fewer arthritics.

The field of drug therapy, in general, has limited value in the arthritic syndrome. Heading the list as regards relief of pain are the salicylates in their various forms but, by and large, they serve only to afford temporary comfort and may have undesirable consequences. In the very early stages of muscular disability their use is not infrequently sufficient to restore a perverted physiology to normal and, upon restoration of function, the physiologic balance of health may be maintained.

Superseding the salicylates in value is arsenic, one of the dozen or more irreplaceable drugs of medicine. Its influence upon metabolism and regeneration of the blood elements is perhaps never more graphic than in some cases of arthritis which may for a time improve so rapidly as to lead to belief that the cure is at hand. Other measures, of limited value, can be grouped under the general caption of those which probably hasten metabolism, such as potassium iodid and the Roentgen ray. Orthoiodoxybenzoic acid, which has recently had a "flair," is a sort of glorified salicylate and has in general not justified the claims made for it by some writers.

Finally, mention must be made in this cavalier review of arthritis, of the importance of coördinating various lines of treatment. It is a fundamental principle in the treatment of disease that the given load must be adjusted to handicapped organs or systems. It is further axiomatic that the restorative powers of Nature alone achieve the processes of convalescence or repair. These facts are too often overlooked, however, in the care of the arthritic, and expectation is often entertained that a drug or injection will restore atrophied muscles or remove the fibrositis and faulty physiology productive of it.

Treatment of the arthritic, with the inevitably long period of convalescence, should be somewhat analogous to the training of an athlete. Professional trainers are unanimous as to the importance of a carefully-balanced programme for their charges. The athlete never runs when he is tired and he rests after his run. Massage further contributes to the efficiency of his normal muscular physiology. How much better the trainer of athletes understands the problems of his protégés than does the average physician the problem of the arthritic. The chronic arthritic is nearly always fatigued but is nevertheless usually asked to undergo at once a variety of

procedures, surgical as well as medical, which often reduce him to an even lower ebb. The writer cannot hope in the brief space here allotted, to discuss the details of the treatment of arthritis in the fullness they deserve. If, however, only one message could be given to this audience it should be an exhortation to maintain a wide-angled viewpoint in considering the rheumatoid problem; to coördinate the various sound measures of therapy critically and more frequently than is usually the case; and to appreciate that at last analysis it is not necessarily the removal of a focus or usually any single agent but rather a restoration of physiology along the many lines indicated which ushers the chronic sufferer from arthritis into channels of recovery. Pessimism has long dominated the attitude of the profession toward the chronic arthritic. A keynote sounded in the brochure of the committee already mentioned, is in the opposite direction, convinced, as many of its members are, of the great value of treatment in this disease. It is of the highest importance that more investigation be carried out on the causes and nature of arthritis. It is of equal importance, however, that there be wider dissemination of what is already known regarding the disease. With the measures now at our command thousands of arthritics throughout the country, probably doomed to wheel-chair invalidism, could be saved from this and often restored to active life if these measures could be intelligently and skillfully applied. Not only are there few other diseases in which intelligent, well coördinated treatment is so urgently required; there are in fact few other chronic diseases for which more can be done.

Arthritis touches more fields of medicine than does any other pathologic state. Its subtleties cannot be learned quickly or easily and it is a favorable augury that this problem is now in process of taking its place with tuberculosis and syphilis as one of the great chapters of medical science. Only when this has been achieved, however, will there arise that wealth of professional equipment which alone is adequate to combat it. We are today in this country in the struggle against arthritis more or less in the position of Trudeau fifty years ago in the fight against tuberculosis. Those of us who have been most interested in this problem are best aware of the inadequacy of individual effort and can only hope that the great mass of right-thinking laymen and medical men will rise, as they have so often done in the past, to the call of distress.

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## ON THE MANAGEMENT OF THE SPASTIC COLON AND MUCOUS COLOPATHY, ESPECIALLY IN HYPERVAGOTONIC PERSONS.\*

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AMONG the common tasks of the general practitioner is that of the treatment of patients suffering from habitual constipation. The therapy of so-called atonic constipation (better called hypokinetic constipation) presents difficulties enough; but the form of habitual constipation in which there is persistent spasm of the colon (hyperkinetic-dyskinetic constipation), often associated with paroxysms in which larger or smaller quantities of mucus are passed from the bowel (so-called "mucous colopathy" or "myxoneurosis intestinalis") is even more obstinate and more difficult satisfactorily to treat, especially when it occurs in patients of outspoken hypervagotonic constitution. It has occurred to me, therefore, that a discussion of this topic might be of particular interest to this audience, which, as I understand it, is composed largely of physicians in general practice.

**The Motility of the Large Intestine.** It would seem desirable to preface my remarks by a brief résumé of existing knowledge of the physiology of colonic motility, since a thorough understanding of the mechanisms of this motility under normal conditions is essential for the interpretation of the abnormal states that are encountered when these mechanisms are disturbed.

You will recall that in the large intestine (as well as in the small bowel) contractions of the longitudinal strands of muscle shorten and widen the tube, whereas contractions of the circular muscle narrow the tube. The so-called *pendulum movements* have the function of mixing the food derivatives intimately with the juices secreted by the digestive glands and also of placing all portions of the contents of the bowel in contact with the surface of the mucous membrane in order that absorption may take place. The *peristaltic movements* have the function of propagating the intestinal contents analward; among these are included the so-called "great colon movements" that come three times in the twenty-four hours, cause the translocation of the contents of the colon over considerable distances. In addition to these peristaltic movements that propagate the contents distalward, there occur, as we now know, *antiperistaltic movements* that provide for retrograde transport of the colonic contents, that is to say that drive the contents oralward rather than analward. It is particularly in the cecum and the

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ascending colon that these antiperistaltic contractions are prominent. As soon as the contents of the ileum are discharged into the cecum, these antiperistaltic contractions begin; they result in the retention of the contents in the cecum and the ascending colon where they not only favor the thorough mixing of the contents but, through the stagnation produced in this part of the large bowel, provide both for the process of bacterial digestion (which is far more important than was formerly thought) and for the absorption of fluids and dissolved substances with consequent concentration of the feces. It is only after the bacterial digestion and the dehydration of the intestinal contents have occurred that these antiperistaltic movements let up; then through peristaltic movements the contents are shoved on into the transverse colon and, later, into the descending colon. The feces remain normally in the sigmoid until, through the movements of defecation, they are discharged to the outside world. In addition to the contractions of the musculature of the colon just described, the smooth muscle of its walls between such contractions is constantly held in a certain degree of tonus (peristolic contraction).

From Roentgen ray studies, it has been shown that barium ordinarily begins to enter the cecum in from one to two hours after it has been swallowed and that the cecum and ascending colon are filled in from two to six hours, whereas it is some ten to sixteen hours before the descending colon and the sigmoid are filled. All the peristaltic movements are a part of the automatic activity of the colon and appear to be innervated by centrifugal impulses from Auerbach's plexus, which in turn is stimulated both mechanically and chemically from the lumen of the bowel and probably also by hormonal influences from the blood. Auerbach's plexus is further influenced by impulses arriving to it through sympathetic and parasympathetic nerve fibers, the innervation of the proximal colon as far as the junction of the first and second thirds of the transverse colon coming from the vagus and the superior splanchnic, that of the distal colon coming from the lower sacral nerves and the inferior splanchnic. The sympathetic fibers carry mainly impulses that depress motility, the parasympathetic (craniosacral autonomic) mainly impulses that increase motility.

The tonus of the musculature of the intestine is believed to be regulated through a plexus in the peritoneal covering of the colon (serosa plexus) without the intermediation of Auerbach's plexus; craniosacral autonomic impulses favor whereas sympathetic impulses inhibit tonus.

Obviously, then, the motility of the colon is a complex affair, dependent upon an intricate set of neuromuscular mechanisms, which must work together in a coördinated or synergistic way for healthy functioning. It is but little wonder that this motility should be easily disturbed, owing either to alteration of its neuromuscular apparatus or to stimuli impinging upon that apparatus.



In habitual constipation, we may find, on the one hand, hypokinetic states of the musculature ("atonic constipation") or, on the other, hyperkinetic states with dyskinetic disturbances of coördination ("spastic constipation"). In not a few cases, there may be hypokinetic phenomena demonstrable in one part of the colon and hyperkinetic-dyskinetic phenomena in another part.

**The Secretory, Digestive, and Absorptive Activity of the Large Intestine.** In contrast with the secretion (succus entericus) of the small bowel, that of the large bowel contains but few ferments and but little of any one ferment. The glands of the small bowel secrete erepsin, arginase, nuclease, lipase, various carbohydrate splitting ferments and enterokinase, which activates trypsin; the glands of the large bowel secrete perhaps a little erepsin, but mainly mucus. The secretory function in both the small and the large intestine is regulated by impulses from Meissner's plexus (in the submucosa), which in turn is influenced by reflex and psychic influences that excite or inhibit.

The digestive activity of the large bowel is due mainly to bacterial action upon the food products rather than to the action of ferments derived from the glands. We are now fairly well informed with regard to the bacterial flora of different parts of the intestine in normal children and adults; in the latter, under ordinary diet, the colonic flora consists largely of *Bacillus coli* and of anaërobic bacteria (Gram negative). Disturbance of this bacterial flora and of bacterial digestion often plays a rôle in the origin of constipation, particularly when there is too much destruction of food residues by the activity of the bacteria, or when because of an abnormal bacterial flora poisons are produced that injure the motor mechanisms.

The absorptive activity of the large bowel is slight in comparison with that of the small intestine, for it is in the latter rather than in the former that the bulk of the soluble products of digestion as well as the digestive juices themselves are absorbed. Still, much water and some diffusible salts are absorbed from the large bowel, particularly from the cecum and the ascending colon where the contents become less fluid before being passed on to the transverse and distal colon.

**The Symptoms and Signs of Spastic Colon and of Mucous Colopathy.** Since heightened irritability of the neural and muscular mechanisms of the colon frequently exists and leads to spasms, to disturbances of coördination of the colonic contractions, and, often, to increased and perverted activity of the glands that secrete mucus, it will be interesting to examine the conditions under which this heightened irritability occurs, to discover the parts of the large intestine most frequently involved, and to discuss the symptoms and signs that most frequently appear. It would take us too far afield to study all types of disturbance of colonic motility; I shall, therefore, not discuss the hypokinetic form of habitual constipation, except insofar

as hypokinetic disturbances may play a rôle in the clinical picture of the form of constipation that is predominantly spastic. Nor shall I attempt to deal with the intestinal spasms that accompany outspoken inflammatory or ulcerative diseases of the colon, but shall rather limit my remarks to the spastic colon that is either a part of a general nervous hyperexcitability or is a neurosis that is predominantly manifested in a local colonic spasm. In these neurotic states, we have to deal with (1) spasm usually of the distal colon; (2) increased peristalsis and antiperistalsis in the cecum and proximal colon with prolonged stasis there and consequent overconcentration of the contents because of dehydration, and (3) increased production of mucus in the form either of jelly-like masses or of inspissated sheets or tubes of mucus. There is thus a profound disturbance of colonic motility (in the sense of hypermotility [both peristaltic and peristolic] and of incoördination of the colonic contractions) combined with a marked disturbance in the secretion and discharge of mucus.

The *subjective symptoms* vary markedly in different patients. It is often difficult to determine in a given case in how far they are due directly to the spastic constipation and in how far to an underlying psychoneurotic state associated with increased parasympathetic tonus (hypervagotonia). The abdominal pains and discomfort are doubtless attributable to the spasm, but the way the patient reacts to these depends much upon the general state of the nervous system. When severe pains accompany the discharge of mucus or precede or follow this, the condition is spoken of as "*colica mucosa*." Affective disturbances are frequently met with in association with colonic spasm and may be very pronounced. There is often a change of mood, the patient becoming depressed and anxious during an attack; but it must be borne in mind that, in predisposed persons, fatigue and depression may precipitate an intestinal spastic state, which in turn can accentuate feelings of sadness and exhaustion that are already present.

The pain may be so very severe and may occur with such extreme suddenness as to excite the idea in a physician who hears the complaint that some malady other than mere spasm of the wall of the colon must exist. In such cases, I have known the pain to be regarded by physicians sometimes as that of gall-stone colic, of renal colic, of acute appendicitis, of gastric or duodenal ulcer, or of angina pectoris! I have known morphin to have been administered to relieve these pains and I have seen patients who have been operated on for a supposed condition of primary surgical urgency within the abdomen, though at the laparotomy nothing more than spasm of the colon could be found!

The constipation complained of may be slight in the milder cases or may be so pronounced in the severer cases as to yield the clinical picture of intestinal obstruction (spastic ileus). In most cases, the

stools are frequent but unsatisfactory; the desire for defecation is strong but the accomplishment is meager. Small fragmented and flattened stools may be passed, but the patient feels after the passage that the bowel has not properly emptied itself; there is lack of that feeling of well-being that follows normal defecation. Often after much strain and discomfort only masses or sheets of mucus will be found to have been discharged. Because of the frequent small stools the patients may say that they have both diarrhea and constipation. After sheets of mucus have been passed, soreness in one or another part of the colon may be felt for a day or two.

On *objective examination* of the patient, the spastic portion of the colon can frequently be palpated as a small firm cylinder. This palpable cord may be very tender; frequently, tenderness can be elicited on palpation throughout the whole course of the colon. On proctoscopic examination, often desirable to rule out carcinoma or ulcer, a spasm at the junction of the sigmoid and rectum with rhythmical contractions can sometimes be directly observed.

The *findings on Roentgen ray examination* are very characteristic. A series of roentgenograms made at intervals after the ingestion of barium reveals the site of the spasm (most often in the transverse or descending colon), the hypermotility of the proximal colon and despite this, the ascendens stasis due to antiperistalsis. There are marked differences in the roentgenograms after barium enemas administered before and after the administration of atropin; the spastic contractions obvious in the former are entirely absent in the latter.

In persons of markedly hypervagotonic constitution, signs of increased parasympathetic tonus in domains other than intestinal may become evident. Thus gastric hyperacidity and pylorospasm are frequently observable; bradycardia and cardiac arrhythmias with precocious systoles are also common. One of my patients suffered from recurrent vagotonic heart block with syncopal attacks coincident with some of his paroxysms of mucous colopathy. Dizziness, transient diplopias, slight dysarthrias, and paresthesias in the lower extremities occasionally accompany exacerbations of the colonic spasm.

The malady is often described as a "mucous colitis," but, as a rule, we deal with a motor and secretory neurosis rather than with actual inflammation. A true colitis, may, it is true, be complicated by paroxysms of spasm and of mucous secretion, and in a few cases of the primary neurosis a secondary colitis may be superimposed; in either case, the feces contain an excess of mucus between the attacks, whereas with ordinary uncomplicated spastic and mucous colopathy there is usually no excess of mucus in the stools in the interparoxysmal periods.

**Differential Diagnosis.** Before deciding upon the diagnosis of a functional disorder, great care should be taken to rule out serious

organic disease. When the mucus is blood-tinged, as it often is, ulcerative processes in the colon or, in older persons, neoplasm may be suspected and should be ruled out by digital exploration of the rectum, by proctosigmoidoscopy, and by roentgenography. Organic stenoses of all sorts are similarly to be eliminated; pericolic adhesions with partial obstruction are common after gynecologic operations and after operations on the gall bladder or appendix and should always be kept in mind as possible causes of clinical pictures resembling the neurosis under consideration. Reflex spasm secondary to diseases of the gall bladder, the appendix and the genital organs should be watched for. Neurasthenic, psychasthenic, hysterical and hypochondriacal trends speak for intestinal neurosis; but it should never be forgotten that neurotic and psychopathic persons may also harbor organic intraabdominal disease. It has been my experience, however, to see mistakes made through the assumption of organic disease and through failure to conceive of the symptoms as being possibly due to a neurosis oftener than in the opposite direction. It is these mistakes that have led so often to superfluous abdominal operations.

**Treatment of Spastic Colon and Mucous Colopathy.** Despite the fact that this malady, uncomplicated, is not dangerous to life, it is responsible for much discomfort, misery and chronic invalidism, and it may be very recalcitrant to treatment. In some cases, fortunately, the response to therapeutic effort is most gratifying, the paroxysms disappearing entirely; in all cases, much can be done to diminish the number and severity of the attacks, provided the patient will adopt the therapeutic measures necessary thereto; but a large number, despite the best treatment known to us, continue to have at least some attacks, especially when subjected to physical, mental or emotional strain. It is not uncommon to meet with relapses after infections, after a bereavement, after familial or other social conflicts, or even after a sudden drop in the Dow Jones averages in Wall Street.

The treatment may be divided into: (1) That of the attacks, and (2) that of the interparoxysmal periods. When an attack is severe, the pain may require immediate relief and for this a dose or two of codein or of pantopon (hypodermically or orally) will usually suffice, especially if the patient will rest quietly in bed, apply heat to the abdomen and in addition, swallow a tablet of atropin (1 mg.) or of novatropin ( $2\frac{1}{2}$  mg.). A subcutaneous injection of 1 mg. of atropin sulphate may be administered instead of the tablet by mouth if a quick effect is desired. This treatment will often be followed by relaxation of the spasm and disappearance of the pain. Purgatives and colonic irrigations are best avoided though if the constipation has been marked and much mucus appears in the stools, one or two colonic irrigations with warm salt solution to which a little sodium bicarbonate has been added may be beneficial. After the acute

symptoms have subsided, the patient may take belladonna, atropin, bellafolin, or novatropin three times a day for a few days and a small intrarectal injection of warm olive oil may be made at 9 P.M. for a few nights.

After an attack, the treatment should be directed toward the prevention of spasm and constipation, toward combating any complicating catarrh of the colon and toward the overcoming of the underlying general neurosis. This treatment should be planned after the making of a general diagnostic survey that will reveal not only every physical disease existent, but also all faulty habits, any peculiarities of personal make-up and any inimical influences in the familial, economic and social environment. No condition, local or general, that could contribute to the invalidism should be permitted to go overlooked.

*Dietotherapy.* There has been a clash of opinion as to the best diet for mucocolopaths with spastic colon. Some, following the lead of von Noorden and Lenhartz, have recommended a *coarse diet* (yielding abundant cellulose residue) inclusive of a large fat ration; such a diet would contain large quantities of foods that mechanically and chemically stimulate the large intestine to contraction (brown bread, bran muffins, leafy green vegetables, cabbage, cauliflower, brussels sprouts, vegetable salads, pickles, turnips, radishes, peas, beans, mushrooms, raw and cooked fruits, honey, nuts, figs and raisins). Such a diet, may in certain instances, especially those in which there is hypokinesis of one part of the colon associated with spasm in another part, be found desirable; but for most mucocolopaths with spasm, I have found it distinctly harmful. I prefer with A. Schmidt, Einhorn, Bastedo, Cawadias, Chase and many others, to use a bland protective diet rather than a stimulating diet in these cases, at any rate until the colonic spasm has been well overcome. As one of my colleagues, Dr. Thomas R. Brown, has emphasized, the coarser diet may be suitable for the intestine of Central Europe, but not for the American intestine when spastic, however desirable when it is hypokinetic.

Such a bland diet may contain meat, chicken, fish, milk, eggs, cream, curds, junket, cottage cheese, butter, with moderate amounts of well-cooked cereals, vegetable purées, stewed fruits and simple desserts. A large glass of acidophilus milk may be taken night and morning. Coffee, tea, alcohol, tobacco and condiments should be restricted. Mineral oil to lubricate and agar-agar to fill the intestine are very advantageous, as they do not irritate the bowel. Abundant water drinking before meals is desirable. In the planning of the diet as a whole, due regard should be given to the general state of nutrition, reducing the caloric intake in the obese, increasing it in the undernourished. When a complicating catarrh of the colon is present, the diet may have to be rigidly protective for a time.

*Pharmacotherapy.* The repeated use of purgatives and long-continued colonic irrigations are, in my opinion, definitely contraindicated. It seems to me probable that future generations will look back upon the vogue of colonic irrigation in our time with amusement similar to ours for the treatment by the black stick *a posteriore!* As long as the spasm of the colon continues, drugs that relax that spasm may be administered with advantage. The most used remedy is belladonna. Ever since Trousseau introduced his famous pill (extracts of leaves and root of belladonna), physicians have given it or tincture of belladonna with benefit to patients suffering from spasm of the colon and the form of constipation that accompanies it. One may, of course, use atropin instead, say 1 mg. tablet on rising and on retiring; or one may give 2 or 3 cg. of bellafolin after each meal. Extract of belladonna may also be given by suppository if desired. Recently, novatropin (homatropin methylbromide) has come into use as a substitute for atropin in lessening spastic states due to parasympathetic hypertonus; it is said to be some fifty times less toxic than atropin though it equals atropin in the reduction of spasm. It is available in  $2\frac{1}{2}$  mg. tablets of which one may be administered on rising and on retiring. For lessening, by drugs, the general hyperirritability of the nervous system, so common in these patients, we may resort temporarily to bromide preparations or to luminal.

Another method of decreasing parasympathetic tonus has lately been introduced. I refer to the administration of Collip's parathyroid hormone along with calcium lactate. Bockus, Bank and Wilkinson have treated a series of 17 patients of mucous colopathy, using about 2 gm. of calcium lactate thrice daily and injecting fifteen units of parathormone (Collip) intramuscularly every third or fourth day. In 12 of the cases there was relief of the local symptoms, and in 10 of the cases the subjective nervous phenomena were lessened. The method would seem worthy of further trial especially in cases that do not respond satisfactorily to treatment with diet and belladonna.

Attention should be paid to the acidity of the gastric contents. When hyperacidity coexists, a blunting powder should be given after meals; achylia is a less frequently associated phenomenon, but if present, is an indication for hydrochloric acid before meals.

When there is much flatulence (often accompanied by palpitation, precordial anxiety, insomnia and depression), a temporary qualitative change of diet (restriction or removal of carbohydrates) may be advantageous. If the intestinal gases and feces are foul-smelling, due to putrefaction of proteins, the addition of acidophilus milk and stewed fruits will be helpful. Some patients, who complain much of "gas," find relief from magnesium perhydrol (1 teaspoonful in water or 1 or 2 half-gram tablets taken thrice daily). In both fermentative and putrefactive processes in the large bowel, the

powder (introduced by Antoine and Rolland of Paris) containing bismuth carbonate, kaolin, and magnesium hydrate, given over a period of several weeks is asserted to be beneficial.

Gout seems to play a rôle in etiology in some patients; cinchophen or neocinchophen may then be helpful along with reduction of the purin intake.

*Physical Therapy.* Warm baths and local heat to the abdomen are preferable to any other form of hydrotherapy or thermotherapy. If massage is used, it should be applied to parts other than the abdomen, or, at any rate, great care should be taken to avoid stimulation of a tender spastic colon. Electrotherapy, though much vaunted, is not indispensable; its effects are chiefly due to suggestion. Nor do I think any special form of balneotherapy or any particular "spa" necessary, though doubtless many patients will find benefit at a well-conducted watering place where there is careful supervision of the patients as regards both mental and physical hygiene. Training in "progressive voluntary relaxation" can be very helpful as the tension in the voluntary musculature decreases, relaxation of the colonic tonus is favored.

*Psychotherapy.* Since a large proportion of mucocolopaths are of neurotic constitution, much help can be given by rational and systematic psychotherapy. First of all, the removal of apprehension of the existence of a severe organic disease (such as cancer of the colon, ulcer, or gall-bladder inflammation) by means of a general diagnostic survey that will convince the patient of its accuracy and thoroughness can be most helpful. Again, a discussion of any other fears, worries or strains to which the patient is subject may be advantageous. Close supervision of the mode of life with definite guidance of activities for a time will make many nervous colopaths grateful to their physicians. In severe cases of mucocolopathy associated with outspoken psychoneurotic or mild psychotic states the pathologic process is not restricted to the vegetative nervous system; for such cases a thorough going rest and upbuilding cure, with isolation, away from the patient's home, and with the aid of a special nurse, occupation therapy and psychotherapy may be desirable, even indispensable, for success.

*Surgical Therapy.* In very obstinate cases, therapeutists with surgical leanings have grown discouraged with nonsurgical therapy and have resorted to exploratory laparotomy in the hope of finding some local cause for the malady; and, finding none, have established an appendicostomy fistula for purpose of irrigation, have resected a part of the colon or removed the whole of it, or have anastomosed the ileum with the sigmoid colon. This lamentable chapter of therapy I dislike to discuss, but I feel it my duty to say that operations of the kind mentioned for uncomplicated spastic colon and mucous colopathy seem to me not only unjustifiable but distinctly reprehensible. The treatment of this functional malady should be

predominantly medical rather than surgical; but it involves not only a knowledge of internal medicine in the narrower sense but also an acquaintance with psychologic and social medicine.

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## CHRONIC ADHESIVE PERICARDITIS IN CHILDHOOD.

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THE problem of pericarditis in children is an interesting and important phase of the study of rheumatic heart disease. Pericarditis is important because of its frequency and its damaging results. Sir John Broadbent<sup>1</sup> states that at the Children's Hospital in London evidence of pericarditis was present in all but 6 of 100 fatal cases of heart disease (1881-1892). Coombs<sup>2</sup> gives the incidence of pericardial lesions in cases of death due to heart disease at the Bristol General Hospital as follows:

Patients dying in the first decade . . . . .	100.0 per cent
Patients dying in the second decade . . . . .	83.3 "
Patients dying in the third decade . . . . .	41.6 "
Patients dying in the fourth decade . . . . .	23.0 "
Patients dying after forty years . . . . .	26.0 "
All patients . . . . .	53.0 per cent



While acute pericarditis is not difficult to recognize, many mild attacks are overlooked, and the after effects are little understood. The disappearance of a friction rub and the absorption of an effusion do not necessarily mark the end of an attack of pericarditis. The process may, and commonly does, go on to productive changes with the formation of nodules and scar tissue,<sup>3</sup> resulting in adhesions which may obliterate the pericardial cavity and bind the heart to the surrounding structures. In this connection, two questions are of special interest: (1) to what extent do the processes started by an attack of pericarditis handicap a child who survives the acute attack? (2) How often does an attack of pericarditis result in adhesions which can be recognized clinically?

In 1898, Sir John Broadbent<sup>4</sup> said that the key to the solution of the problem of adherent pericardium seemed to lie in the investigation of cases of pericarditis which could be kept under observation while going on the formation of adhesions.

The present study\* is an attempt to follow, over as long a period as possible, 51 children who have had acute pericarditis or in whom a tentative diagnosis of adherent pericardium has been made. The cases were taken as they came without any attempt at selection, all those children who were known to have a pericardial effusion or friction rub and all those who presented signs suggesting adherent pericardium. The only cases omitted were those who were seen but once in the Clinic and those who were never followed after discharge from the ward. Some of the children have been under observation for a relatively short period; others have attended the Clinic for ten years; many have been admitted to the hospital, not once, but repeatedly; most of them have spent months in convalescent homes; a few have been lost.

The study is obviously incomplete in many ways. It cannot include all those children who have had pericarditis, for it is often impossible to obtain an accurate history; friction rubs are often transitory and pericardial effusions may be described as "pleurisy," "heart trouble," "pneumonia" or "water on the chest." In many cases it is impossible to follow patients over a long period of years. Finally, it is difficult to interpret physical signs, and it is usually impossible to check clinical findings with postmortem records.

Fifty-one children are included in the present study. In 39 of the cases there is a definite record of some pericardial involvement. In 2 of these cases, both of which lacked history of an attack of acute pericarditis, complete obliteration of the pericardial sac with extensive adhesions was found at autopsy; in one a tentative diagnosis of adherent pericardium was made during life; in the other the autopsy finding was quite unexpected. In the remaining 11

\* This study is based upon the records of the First Medical Division and the Children's Cardiac Clinic of the New York Hospital. Services of Dr. Lewis A. Conner and Dr. Joseph C. Roper.

cases a tentative diagnosis of adherent pericardium was made on the basis of signs and symptoms. Twenty-two cases are under observation at the present time, 21 have died (with 5 autopsies) and 8 have been lost. Before discussing the course of the disease or the physical signs, it is convenient to summarize the acute outbreaks in each child's history. No child who died during an acute attack of pericarditis is included in this series; these are all children who are alive at present or who died after the acute process had subsided. An attempt has been made to include information as to the valvular damage, indicating the lesion diagnosed by initials (M. for mitral, A. for aortic, I. for insufficiency, S. for stenosis) and to give the condition of the child when last seen. Unless otherwise noted, as dead or lost, the children are under observation at the present time.

## TABULATION OF CASES.

1. Augustine A.:
  - 11 years, mild rheumatism.
  - 13 " *pericarditis with effusion*; M.S.
  - 16 " rheumatic fever; A.I. and possibly M.S.
  - 17 " rheumatic fever; A.I., M.S. and adhesive pericarditis; condition poor; dyspnea, tachycardia and cyanosis. Died.
2. Salvatore B.:
  - 6 years, dyspnea and palpitation.
  - 7 " *pericarditis with effusion*; M.S.; died 3 months later.
3. Harry B.:
  - 5 years, said to have "heart trouble."
  - 6 " tonsillectomy for frequent sore throats.
  - 7 " rheumatic fever (2 attacks); precordial pain; M.S.
  - 10 " *pericarditis with effusion*.
  - 13 " occasional joint pains for 3 years; improving.
4. Thomas B.:
  - 4 years, "fever;" M.S.
  - 7 " *pericarditis with effusion*; large heart and liver.
  - 8 " died.
5. David C.:
  - 5 years, rheumatic fever for 2 months; growing pains for next 3 years; scarlet fever (exact age unknown).
  - 8 " rheumatic fever for 4 months; "heart trouble."
  - 10 " rheumatic fever.
  - 12 " tonsillitis; rheumatic fever; *pericarditis with effusion*; M.S. and A.I.
  - 13 " purpura or erythema; febrile attacks.
  - 14 " auricular fibrillation and cardiac decompensation.
  - 15 " three febrile attacks; died.
- 5a. Jimmy C.:
  - 7 years, rheumatic fever.
  - 9 " dyspnea.
  - 10 " dyspnea, little edema, large liver; M.I. and M.S.; *pericardial friction rub*.
  - 11 " very large liver, ascites; M.S. and A.I.
  - 12 " died.

6. Margaret C.:
  - 5 years, chorea.
  - 7 " chorea; tonsillectomy; M.I.
  - 9 " chorea.
  - 11 " chorea; *pericarditis with effusion*; nodules; M.I.
  - 12 " chorea; nodules; M.I. and A.I.
  - 14 " chorea.
8. James D.:
  - 12 years, indefinite history of growing pains; tonsillectomy; M.S.
  - 13 " ascites; large liver; M.S. and A.I.
  - 14 " died.
9. Armande de R.:
  - 7 years, sore throats; vague pains; tonsillectomy.
  - 8 " chorea; pleurisy (or pericarditis?) with effusion.
  - 10 " M.S., signs of adhesive pericarditis; condition poor and growing worse.
10. Santos, D.:
  - 6 years, scarlet fever followed by joint pains and tachycardia; *pericardial friction rub*; M.I.
  - 7 " M.S. and A.I.
  - 8 " condition rather poor.
11. Agnes E.:
  - 6 years, acute appendicitis with appendectomy and drainage; 3 months later tachycardia and cough; large heart; M.S.
  - 8 " cardiac decompensation; probably adhesive pericarditis. Died, February, 1929, apparently of cardiac failure.
12. Edward E.:
  - 8 years, joint pains; *pericarditis with effusion*; M.S.
  - 10 " two mild rheumatic attacks.
  - 22 " in good health; M.S.
13. Edward F.:
  - 4 years, tonsillectomy.
  - 10 " abdominal pain ("chronic appendicitis"), M.I. Six months later rheumatic fever, M.I. and possibly M.S.
  - 12 " *pericarditis with effusion*; M.S. and possibly A. I. Died 3 months later (autopsy).
14. Morris F.:
  - 10 years, rheumatism and "heart trouble."
  - 15 " *pericarditis with effusion*; in good condition 6 months later. Lost.
15. Veronica F.:
  - 10 years, chorea.
  - 11 " "heart trouble."
  - 12 " growing pains, "heart trouble," in bed 9 months; M.S.
  - 14 " growing pains; bronchopneumonia; M.S. and possible A.I., adhesive pericarditis.
16. Sidney G.:
  - 10 years, history of frequent rheumatic and abdominal pains.
  - 11 " nodules; M.S. and A.I.
  - 12 " growing pains, abdominal pain.
  - 14 " growing pains; rheumatic fever.
  - 15 " rheumatic fever; M.S. and A.I., adhesive pericarditis.(?)

## 17. Frank G.:

- 8 years, rheumatic fever.
- 9 " *pericarditis with effusion* for 6 weeks; tonsillectomy.
- 12 " pleurisy with effusion; M.I. and A.I.
- 15 " *pericarditis with effusion* for 6 weeks.
- 16 " fever, *pericardial friction rub*.
- 17 " *pericarditis with effusion* for 1 month.
- 20 " well and working.

This boy has recently developed a subacute bacterial endocarditis with *Streptococcus viridans* in his blood. Died.

## 18. Jeanette K.:

- 6 years, scarlet fever.
- 7 " sore throats, muscle pains, tonsillectomy.
- 8 " rheumatism, *pericarditis with effusion*; possible M.S. Six months later enormous heart, cardiac failure, M.S.
- 10 " large heart and liver, auricular fibrillation; died.

## 19. Rita K.:

- 7 years, *pericarditis with effusion*; fever for 18 months; M.S.
- 8 " nodules; M.S. and possibly A.I.
- 9 " large heart and liver, ascites, decompensation.
- 10 " no ascites, fair compensation.
- 11 " decompensation and ascites; M.S. and A.I., improvement with rest and digitalis.
- 12 " Died, March, 1929, of cardiac failure and terminal bronchopneumonia. Auricular fibrillation was present for the last three weeks of life.

## 20. Ida K.:

- 10 years, "heart trouble" for 3 years, *pericardial friction rub*; M.S. and M.I., enormous liver, ascites.
- 11 " no ascites, signs of adhesive pericarditis.
- 13 " died very suddenly after 2 weeks of moderate cardiac decompensation.

## 21. Annie K.:

- 4 years, rheumatism.
- 5 " rheumatism, "heart trouble."
- 6 " rheumatism, measles.
- 7 " *pericardial rub and effusion*; M.S. and M.I., muscle pains, nodules and protracted fever.

## 22. Bernard L.:

- 7 years, chorea (history of measles, pleurisy and pneumonia).
- 8 " rheumatic fever, pneumonia, *pericardial friction rub*; M.S.
- 9 " rheumatic fever.
- 10 " growing pains.
- 11 " rheumatic fever; M.S.

## 23. Edward L.:

- 5 years, "grippe" followed by joint and muscle pains.
- 6 " "heart trouble."
- 7 " *pericarditis with effusion*.
- 8 " pain in left chest.
- 9 " poor condition, large overacting heart. Lost.

## 24. Anna M.:

- 7 years, scarlet fever.
- 9 " tonsillitis.
- 11 " rheumatism followed by "pleurisy" with cough and dyspnea.
- 13 " *pericardial friction rub*; A.I. and A.S.
- 14 " tonsillectomy. Lost.

25. Henry M.:
  - 10 years, tonsillitis; precordial pain; M.S.
  - 12 " rheumatism; nodules.
  - 13 " erythema multiforme; signs of adherent pericardium.
  - 15 " occasional rheumatic pains.
26. Paul M.:
  - 16 years, sore throat; rheumatism; pericardial friction rub; M.S.
  - 17 " in good condition. Lost.
27. Joseph Mo.:
  - 10 years, cardiac pain and dyspnea; in bed for 1 year.
  - 11 " cardiac pain and dyspnea; in bed for 2 weeks.
  - 13 " cardiac pain and dyspnea; in bed for 4 months.
  - 15 " cardiac decompensation with edema and dyspnea; venous thromboses; M.I., M.S., A.I. Died (autopsy).
28. Joseph Mu.:
  - 8 years, tonsillitis; scarlet fever; normal heart.
  - 11 " rheumatic fever.
  - 14 " rheumatic fever followed by dyspnea and tachycardia.
  - 15 " *pericardial friction rub and possible effusion*; M.S. and A.I.; in good health six months later.
29. Doris O.:
  - 3 years, rheumatic fever.
  - 4 " rheumatic fever.
  - 5 " rheumatic fever.
  - 6 " rheumatic fever; M.S.
  - 7 " *pericarditis with effusion*.
  - 8 " "acute myocarditis;" pericardial friction rub.
  - 9 " tonsillectomy.
  - 11 " rheumatic fever.
30. Helen P.:
  - 9 years, rheumatism; tonsillectomy; M.S. and M.I.
  - 10 " rheumatism; *pericardial friction rub*; M.S. and A.I.
  - 11 " acute bronchitis; *possible pericarditis with effusion*.
  - 12 " *pericardial friction rub*; enormous heart.
  - 14 " Died.
31. Sylvia P.:
  - 3 years, rheumatism; M.I.
  - 4 " otitis media; growing pains.
  - 5 " rheumatism; *pericardial friction rub*; M.I. and possibly M.S.
  - 6 " *pericarditis with effusion*; pertussis.
  - 7 " rheumatism; 6 months later fever, tachycardia, *pericardial friction rub* and cardiac failure with general anasarca. Died (autopsy).
32. Rocco P.:
  - 3 years, pneumonia.
  - 4 " *pericardial friction rub*; M.S.; died a few months later.
33. Rosa R.:
  - 12 years, *pericarditis with effusion*; large heart; no murmurs.
  - 13 " good health; A.I. Lost.
34. Rosie R.:
  - 4 years, "stomach trouble" with large heart, liver and spleen; M.I.
  - 5 " died with general edema.
35. Joseph R.:
  - 8 years, rheumatism; large heart; *pericardial friction rub*; M.I.
  - 9 " enormous heart; M.I. and possibly A.I.
  - 10 " died.

36. Helen R.:  
 5 years, abdominal pain, malaise and dyspnea; 6 months later increased dyspnea, large heart and liver; M.S. and A.I.  
 6 " dyspnea; *pericardial friction rub*; later ascites, edema, auricular fibrillation. Died (autopsy).
37. Isadore R.:  
 7 years, tonsillitis.  
 8-9 " tonsillitis, vague pains.  
 12 " rheumatic fever.  
 13 " *pericardial friction rub*; M.I.  
 15 " tonsillectomy; heart not enlarged, systolic murmur. Lost.
38. Louis R.:  
 6 years, torticollis; frequent sore throats.  
 9 " tonsillectomy.  
 14 " *pericarditis with effusion*; M.S. and A.I.  
 19 " in good health.
39. Miriam S.:  
 3-(?) years, joint pains, nodules, scarlet fever (exact age unknown).  
 14 " *pericardial friction rub*; large heart and liver; M.S. and A.I. Died.
40. Paul S.:  
 6 years, tonsillectomy.  
 7 " rheumatism.  
 8 " rheumatism; nodules; M.S. and adhesive pericarditis; swollen liver.
41. Nettie S.:  
 3-10 " frequent tonsillitis and vague pains; tonsillectomy.  
 9 " fever for a few days.  
 11 " "said to have a weak heart."  
 13 " *pericardial friction rub*; dyspnea and tachycardia; M.S.
42. Michellina S.:  
 4 years, *pericarditis with effusion*; later bronchopneumonia.  
 5 " M.S.  
 6 " M.S.
43. Hazel S.:  
 4 years, rheumatic fever.  
 7 " influenza.  
 11 " tachycardia; large heart; M.S.; pertussis.  
 13 " onset of auricular fibrillation.  
 17 " very large heart with dilated left auricle.
44. Julius T.:  
 6 years, tonsillectomy for frequent sore throats.  
 7 " bronchitis; M.I. and A.I.  
 8 " otitis media; occasional rheumatic pains.  
 10 " *pericarditis with effusion*; A.I. and possibly M.S.  
 14 " severe rheumatic fever; A.I.
45. Arthur T.:  
 8 " said to have "heart trouble."  
 12 " occasional fever and precordial pain, dyspnea; M.S. and M.I.  
 13 " fever; tonsillectomy.  
 18 " acute cardiac decompensation; flutter and fibrillation. Died (autopsy).

46. Andrew T.:  
 3 years, rheumatism.  
 4 " cough and nausea for 3 months.  
 7 " nosebleeds.  
 14 " fever; A.I.  
 16 " signs suggesting adhesive pericarditis.
47. Dominick T.:  
 11 years, diphtheria.  
 12 " rheumatic fever; M.S. and A.I.; six months later *pericarditis with effusion*.  
 13 " died.
48. Fred V.  
 8 years, chorea.  
 14 " chorea.  
 15 " large heart; possible adhesive pericarditis; M.S. Lost.
49. William W.:  
 ? years, grippe, measles, growing pains, scarlet fever.  
 8 " tonsillectomy.  
 15 " *pericarditis with effusion*; nodules; A.I.  
 16 " very large heart.  
 18 " living; unable to attend Clinic.
50. Frederick W.:  
 ?-12 years, repeated attacks of chorea, tonsillitis and rheumatism.  
 13 " tonsillectomy; M.I. and A.I.  
 17 " *pericarditis with effusion*; M.S. and A.I. Lost.

**Clinical Course.** In reviewing these cases several important facts stand out. The rheumatic infection usually appeared at an early age, and in the majority of cases was characterized by repeated acute attacks. In some cases the exact age of onset is unknown, because a child at the time of the first examination was found to have definite signs of mitral stenosis but no history which could be interpreted as evidence of rheumatism. In other cases, the history obtained from the parents was indefinite, and it seemed probable that "growing pains" had been present for some time before attention was called to the child's sickness. The exact age at which the rheumatic infection first appeared is often unknown, but the infection was present at, or before:

Years.	Cases.
3 . . . . .	6
4 . . . . .	5
5 . . . . .	5
6 . . . . .	5
7 . . . . .	8
8 . . . . .	6
9 . . . . .	2
10 . . . . .	6
11 . . . . .	2
12 . . . . .	4
After 12 . . . . .	1

In addition to the more acute manifestations of the disease, many of the children had mild growing pains and occasional periods of low-grade fever of which accurate record is usually lacking. The

early appearance and the severity of the infection are important because it is in the severe infections that pericarditis is most common and also that the heart is most damaged. In considering the prognosis and the course of the disease one should be able to differentiate between the results of pericarditis and those of infection elsewhere, but unfortunately this is rarely possible.

In 26 cases, an attack of pericarditis seemed to be a definite turning point, the beginning of a train of unfavorable signs and symptoms which became progressively worse and which usually led to death within a short time. Only 1 child in this group is known to be alive for more than three years after the acute attack; 19 are dead and 7 are growing worse.

Of the 21 who died, all had symptoms and signs of cardiac insufficiency. In practically every case the apparent cause of death was cardiac failure; often the exact cause could not be determined. One patient died of pneumococcus endocarditis and septicemia, 1 of bronchopneumonia, 1 during an attack of acute rheumatic fever, and 1 died suddenly. In each of these cases, there was marked cardiac decompensation before death. In all the other cases, death was ascribed to the cardiac condition, but in no case could it be said that the pericarditis was directly responsible. In 5 of these cases, there was no definite record of acute pericarditis, but, in 4 of these, there was a history of an acute illness which was probably pericarditis and a tentative diagnosis of adherent pericardium was made during life, and in one case was confirmed postmortem. In the fifth case in which there was no history of pericarditis, complete obliteration of the pericardial sac was an unexpected autopsy finding. In the remaining cases, death followed the acute attack after an interval of from three months to three years. These cases with the associated valvular lesions and evidences of myocardial damage are summarized in Table I.

These were all children who "recovered" from acute pericarditis, but they were never well. Clinically they showed evidence of continued infection and progressive cardiac damage; fever, tachycardia, pain, leukocytosis, dyspnea, weakness and edema in varying degrees. All of them had evidence of endocardial damage, signs of mitral stenosis in every case, of aortic insufficiency as well in 12 cases, and of mitral stenosis, aortic insufficiency and stenosis, and tricuspid stenosis in 1 case. In every case there were symptoms of cardiac failure, and in all but 5 cases, in which the records are incomplete, there were signs of myocardial damage. (See Table I.) These signs consisted of abnormal electrocardiograms or of microscopic changes demonstrated at autopsy. The abnormal electrocardiographic signs were abnormalities of the *T* wave, low voltage, and widening, notching and slurring of the *Q-R-S* group. The 5 cases which came to autopsy showed complete obliteration of the pericardial sac and adhesions to the surrounding structures. In 4 of



these, the diagnosis was made before death. It has been said that adherent pericardium is regarded as the usual cause of cardiac failure in rheumatic children,<sup>5</sup> but from these few cases it would appear that a severe and protracted infection with a pancarditis was at least as important as interference with the work of the heart due directly to the adhesions.

TABLE I.

Case No.	Name.	Age at death, yrs.	Time before death at which pericarditis was noted.	Valvular lesion.	Evidence of myocardial damage.
1	Augustine A.	17	4 yrs.	M.S. and A.I.	EKG.
2	Salvatore B.	7	3 mos.	M.S. ?	
4	Thomas B.	8	1 yr.	M.S.	
5	David C.	15	3 yrs.	M.S. and A.I.	Fibrillation; EKG.
5a	Jimmy C.	12	2 yrs.	M.S. and A.I.	EKG.
8	James D.	14	?	M.A. and A.I.	EKG.
11	Agnes E.	8	2 yrs. ?	M.S.	
13	Edward F.	12	3 mos.	M.S. and A.I.	EKG.; autopsy.
17	Frank G.	20	11 yrs.	M.I. and A.I.	EKG.
18	Jeanette K.	10	2 yrs.	M.S.	Fibrillation.
19	Rita K.	12	5 yrs.	M.S. and poss. A.I.	
20	Ida K.	13	3 yrs.	M.S.	EKG.
27	Joseph Mo.	15	3 yrs. ?	M.S., T.S., A.I. and A.S.	EKG.; autopsy.
30	Helen P.	14	2 yrs.	M.S. and A.I.	EKG.
32	Rocco P.	5	Few mos.	M.S.	
34	Rosie R.	5	?	M.I.	
35	Joseph R.	10	2 yrs.	M.S. and A.I.	Autopsy.
39	Miriam S.	14	3 mos.	M.I. and M.S.	EKG.
45	Arthur T.	18	?	M.S. (A.I.)	EKG.; autopsy.
47	Dominick T.	13	6 mos.	M.S. and A.I.	
31	Sylvia P.	7	18 mos.	M.S.	EKG.; autopsy.

Seven children who are still living have become progressively worse following an attack of pericarditis. These cases are summarized in Table II and are similar to those discussed above except for the fact that they are still alive. In passing, it may be noted that the longest interval following the pericarditis in these cases is less than four years.

TABLE II.—LIVING CASES THAT HAVE BECOME PROGRESSIVELY WORSE.

Name.	Age, yrs.	Pericarditis at age of, yrs.	Valvular lesions.	Electrocardiogram.
Santos D. . . . .	7	6	M.S. and A.I.	Abnormal.
Armande de R. . . . .	10	8 ?	M.S. and A.I.	Abnormal.
Doris O. . . . .	11	7	M.S.	Abnormal.
Annie K. . . . .	7	7	M.S.	Abnormal.
Michellina S. . . . .	6	4	M.S.	Abnormal.
Paul S. . . . .	8	?	M.S.	Abnormal.
William W. . . . .	18	15	A.I.	?

Twenty-four cases remain to be considered. Of these 8 were lost within two years. When last seen, 2 were in poor condition and were steadily growing worse, 2 were in fair shape, and the remaining 4 were in good health and living reasonably normal lives.

Two boys are in really good health and are working as clerk, fourteen (Edward E.) and five (Louis R.) years respectively, after a severe attack of pericarditis with effusion. One of these boys had two very mild attacks of rheumatism, the other has not been sick since he had pericarditis. Both have valvular lesions, mitral stenosis in one case, and mitral stenosis and aortic insufficiency in the other. The one who has been examined recently has no physical signs which would suggest the presence of adherent pericardium. One other boy (Frank G.) has been in fairly good condition and is working as draftsman in spite of the fact that he has had three severe attacks of pericarditis with effusion, the first eleven and the last three years ago. He has a large heart with the classic signs of aortic insufficiency, but no evidence of adherent pericardium. Very recently there has appeared evidence of subacute bacterial endocarditis. Two younger boys are in fair condition and seem to be improving. One (Andrew T.) has signs which might be interpreted as due to adherent pericardium; the other (Harry B.) had an effusion three years ago, but at the present time has no signs to suggest adherent pericardium. One girl (Hazel S.), who is believed to have an adherent pericardium, is living an active life in spite of the fact that she has had auricular fibrillation for three years and that she has a heart so large that it practically fills her chest. She has not had frequent rheumatic attacks.

Finally, there are 10 children who are in rather poor condition, who have had repeated attacks of rheumatic fever or chorea—in every case at least one attack within the past year—and who all have some evidence of pericardial involvement. The future of these children seems doubtful.

The following table summarizes the fate of these 51 children as far as it is known. While conclusions based upon the observation of such a small series of cases are worthless for statistical purposes, the observations indicate that rheumatic pericarditis in children is a very serious thing and that even with recovery from the acute attack, the prognosis is bad.

TABLE III.—PROGRESS OF 51 CASES OF ADHESIVE PERICARDITIS.

	No.
Patients dead within 4 yrs. . . . .	21
Patients growing progressively worse (6 mos. to 3½ yrs.) . . . . .	7
Patients living reasonably normal lives . . . . .	6
Patients in poor condition whose future seems doubtful . . . . .	9
Patients lost . . . . .	8
Total . . . . .	51

**Complications. Ascites.** Twelve patients in this series had marked ascites and enlargement of the liver, but in only 2 cases was the accumulation of liquid so great as to require repeated tapping. In each case the ascites was associated with cardiac decompensation, and in only one case did it seem out of proportion to other evidences of cardiac failure. The important features of Pick's disease or polyserositis are enlargement of the liver, ascites, slight jaundice, weakness and dyspnea; special cardiac symptoms are lacking, but obliterative pericarditis is present. In the cases collected by Pick<sup>6</sup> and by Cabot<sup>7</sup> the ascites lasted for several years, marked cardiac enlargement was usually lacking and the pericarditis was either tuberculous or of unknown etiology. In the cases in this series the ascites and enlargement of the liver may have been of a similar nature, but the picture was that of cardiac failure rather than that of cirrhosis or pseudocirrhosis of the liver. The appearance of ascites in these cases was of more serious import than in the cases collected by Cabot.

**Auricular Fibrillation.** Auricular fibrillation was observed in 6 of the children in this series. In 4 cases, it appeared as part of a general breakdown preceding death; in 1 case, it was temporary, and the patient subsequently lived with a sinus rhythm for two years; in 1 case it has been present for the past four years. In 2 cases, an attempt was made to restore sinus rhythm by the use of quinidin; both attempts were unsuccessful, although in 1 case the change occurred, but lasted for a few hours only. In 1 case, the fibrillation appeared only after digitalis had been given to a patient with flutter. The diagnosis of mitral stenosis was made in all these cases, and in one that of aortic insufficiency as well. In 2 cases obliterative pericarditis was demonstrated at autopsy.

TABLE IV.—AURICULAR FIBRILLATION IN ADHESIVE PERICARDITIS.

Name.	Age, yrs.	Duration of A.F.	Age at onset of pericarditis, yrs.
David C. . . . .	Died at 15	1 yr.	12
Jeanette K. . . . .	Died at 10	Few wks.	8
Ida K. . . . .	Died at 12	2 wks. (at 10 yrs.)	10
Helen R. . . . .	Died at 6	3 wks.	5 (autopsy)
Hazel S. . . . .	Living at 17	4 yrs.	?
Arthur T. . . . .	Died at 18	2 mos. (flutter)	? (autopsy)

**Bacterial Endocarditis.** Bacterial endocarditis was present in 2 cases. In one, the infecting organism was a Group IV pneumococcus and the course was acute; in the other, a *Streptococcus viridans* was present on blood culture and the patient is running the course of a case of subacute bacterial endocarditis.

**Physical Signs.** It is said that the diagnosis of adherent pericardium is more often missed than made,<sup>8</sup> and that of all important conditions adherent pericardium is the one most likely to come to the

autopsy table undiagnosed.<sup>9</sup> The reasons for this are several. In the first place, adhesions between the two layers of the pericardium may give no symptoms and no signs. In the second place, even when there are adhesions to the surrounding structures, there is no single pathognomonic sign, and every sign considered typical of this condition has been found in the absence of any pericardial involvement. It is commonly said that even though distinctive signs be lacking, the condition is to be suspected when there is a history of acute pericarditis or when the evidence of cardiac failure seems out of proportion to the amount of valvular damage. The group of patients with symptoms of failure out of proportion to the signs is hard to identify in children, and seems to consist of those who have fever and other evidence of active infection and those in whom the cardiac failure is a terminal condition. Every child with rheumatic pericarditis is almost certain to have endocarditis and myocarditis as well, and it is difficult if not impossible to estimate the importance of the pericarditis in any single case.

The physical signs are numerous, but fall into several groups: fixation of the apex impulse and of the outline of cardiac dullness, abnormal systolic retractions produced by the pull of the heart on the surrounding structures, interference with the normal respiratory movements because of adhesions to the diaphragm or the ribs, variations in the arterial or venous pulse, and modifications of the heart sounds. These signs vary with the position, extent and density of the adhesions, and in children are modified by the elasticity of the chests.

In discussing physical signs only those (24) cases will be considered in detail which have been under observation in the Clinic since the present study was started. In the past two years all physical examinations made in the Clinic have been made with the possibility of adherent pericardium specially in mind; all children have been examined repeatedly; and in as many cases as possible confirmatory evidence has been sought in Roentgen ray and electrocardiographic studies.

The first and most striking thing in reviewing these cases is that with few exceptions the children are in poor condition; usually they are in Class II-B\* with longer or shorter periods in Class III.\* They are children who are never very well and who are often very sick, but the health over a period of years does not seem to be directly related to the severity of the acute attack of pericarditis. Second, almost without exception they are children with very large hearts. In most cases the apex is in the fifth, sixth or seventh space at or near the anterior axillary line, and there is some enlargement to the right as well. With such large hearts, it is not easy to detect by physical examination such signs as lack of change in the cardiac dullness

\* Nomenclature for cardiac diagnosis approved by the American Heart Association.

upon respiration or fixation of the apex impulse on change of position. In almost every case, the heart seemed to shift its position to some extent, and usually this shift could be demonstrated by fluoroscopic examination. With elastic chests, however, some shifting might occur even with extensive adhesions. Electrocardiograms taken in three positions have not seemed of definite value,<sup>10,11</sup> in some cases they indicated that the heart was freely movable, in others that it was fixed. In one case in which there was electrocardiographic evidence of a movable mediastinum autopsy revealed obliteration of the pericardial cavity and adhesions to all the surrounding structures. In another case, the electrocardiogram indicated that the heart was fixed, a finding which was confirmed at autopsy.

Systolic retractions of the interspaces alone are common and without significance, being present when a large heart is in direct contact with the chest wall without the usual intervening pad of lung. Systolic retractions of the sternum and costal cartilages or of the eleventh and twelfth spaces in the posterior axillary line are usually caused by adhesions between the heart and the chest wall or between the heart and the diaphragm.<sup>1</sup> Retraction of the costal cartilages and sternum was present in 14 out of 24 cases, and in 6 of these retraction was noted posteriorly as well. Adhesions between the heart and the diaphragm may cause interference with the normal respiratory movements,<sup>12</sup> detected with the help of the fluoroscope or noted as a drawing-in of the epigastrium on inspiration.

Diastolic collapse and abnormal filling of the neck veins are of very doubtful significance. Pulsus paradoxus, present on quiet respiration, is a suggestive sign,<sup>13</sup> and a sign which may be present on one examination but not on the next. Dilated veins over the front of the chest seem to be relatively common, and are probably caused by some interference with the venous return. In general the character of the pulse depends less upon the presence of adherent pericardium than upon other factors such as the predominant valvular lesion.

Pericardial adhesions can, by drawing on different parts of the heart, modify the heart sounds or cause murmurs which may simulate those of any valvular lesion. In this group of children a third heart sound was not uncommon, and when present was usually associated with a palpable shock. In no case did this seem to be an outstanding feature, and even if it had been it would not necessarily have pointed to the presence of pericardial adhesions, as an exaggerated sound and shock are said to be common in three conditions—mitral stenosis, aortic insufficiency and adherent pericardium.<sup>14,15,16</sup> The murmurs heard were interpreted as the result of valvular damage, but when a murmur appeared following an attack of pericarditis, the question arose whether this murmur represented new damage to the endocardium or whether it was related to the peri-

carditis. In 4 patients, all of them young children, signs of mitral stenosis appeared within a short time after pericarditis with effusion,

TABLE V.—ANALYSIS OF PHYSICAL SIGNS OF 24 CASES OF PERICARDITIS

Interval between pericarditis and most recent examination	4 yrs.	3 yrs.	3 yrs.	2 (?) yrs.	1 yr.	2 (?) yrs.	3 yrs.	3, 5, 11 yrs.	3 yrs.	?	6 mos.	4 yrs.	18 mos.	6 mos.	2 yrs.	?	?	?	3 (?) yrs.	4 yrs.	?	5 mos.	3 yrs.	5 yrs.	Total positive.
History of acute pericarditis	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	14
Increased size of heart	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	22
Systematic retraction:																									
Anterior	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	14
Posterior	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	6
Fixation of heart	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	9
Interference with respiration	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	6
Pulsus paradoxus	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	5
Dilated veins	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	10

\* indicates present.      - indicates absent.

Reading across, one sees how often each sign was present; reading up and down, one sees which combinations of signs were present in individual cases.

but this does not mean that the presystolic murmur was caused by the pericarditis:

Armande deR.: Pericarditis with effusion (?) at 8 years; signs of adherent pericardium and of M.S. at 9 years.

Santos D.: Pericardial rub at 6 years; signs of M.S. at 7 years.

Jeanette K.: Pericardial effusion and possible M.S. at 8 years; definite signs of M.S. 6 months later.

Michellina S.: Pericarditis with effusion at 4 years; signs of M.S. at 5 years.

Adherent pericardium may, in the absence of aortic insufficiency, cause a high-pitched, early diastolic murmur, heard at the aortic area and transmitted down the sternum toward the apex. In one case in this series such a murmur was present together with water-hammer pulse, Duroziez murmur and capillary pulse. At autopsy, a normal aortic valve was found and the clinical diagnosis of aortic insufficiency was changed to a postmortem diagnosis of adherent pericardium.<sup>17</sup> In 4 cases in the series the clinical diagnosis was confirmed, and both aortic insufficiency and adherent pericardium were found at autopsy. In 7 of the other 16 cases presenting an "aortic diastolic murmur" this murmur appeared following an attack of pericarditis and might be caused by pericardial adhesions or by disease of the aortic valve:

Augustine A.: At 13 years had acute pericarditis with effusion and signs of M.S.; at 17 years had signs of A.I., adhesive pericarditis and M.S. Died.

Jimmy C.: At 10 years had pericardial rub and signs of M.S.; at 11 years signs of M.S. and A.I.; died at 12 years; no autopsy.

- Margaret C.: At 11 years had pericarditis with effusion, signs of M.I.; at 13 years has signs of A.I.
- Frank G.: Had pericarditis with effusion at 9, 15 and 17 years; signs of A.I. from 12 years; died at 20 years.
- Rita K.: At 7 years had pericarditis with effusion and signs of M.S.; at 8 years had signs of M.S. and possibly A.I.; at 12 years had signs of M.S., A.I. and adhesive pericarditis. Died.
- Anna M.: At 11 years had "pleurisy;" at 13 years had signs of A.I. Lost.
- Rosa R.: At 12 years had pericarditis with effusion, no murmurs; at 13 years had signs of A.I. Lost.

**Summary.** From a study of pericarditis in fifty children with rheumatic heart disease the following statements seem justified:

Rheumatic pericarditis appears in association with a severe infection and one which appears early in life. The prognosis is bad; more than one-third of those children who recover from the acute attack are likely to die within three years; probably one-half will die within five years; few will ever lead normal lives.

Pericarditis is associated with valvular disease, usually with mitral stenosis, often with aortic insufficiency, and is usually merely one part of progressive heart disease.

Marked cardiac enlargement is the rule; auricular fibrillation may be present. Ascites appears as part of a general breakdown, and when present presents a somewhat different picture from that described as Pick's disease.

Some physical signs are likely to be present except in those cases where there is little enlargement of the heart and where the general health is unimpaired. These signs may appear within a few months following an acute attack of pericarditis, but their absence does not necessarily exclude the presence of chronic adhesive pericarditis.

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## SODIUM RICINOLEATE IN ALLERGIC DISEASE OF THE INTESTINAL TRACT.

### PRELIMINARY REPORT.

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For the last year and a half one of us (M.) has been treating patients with intestinal symptoms, associated with hypersensitization to intradermal injections of heat-killed intestinal bacteria, by the daily administration of castor oil. The theory on which the castor oil has been used is based on the fact, first demonstrated by Larson, that sodium ricinoleate is capable of neutralizing bacterial poisons. Our patients presented many symptoms suggesting an intoxication (the so-called "intestinal autointoxication"), and we were failing frequently to give them relief. As oils are converted into soaps in the intestines, we felt that there was a possibility that bacterial poisons, if present, might be neutralized by the ricinoleates formed in the intestines. Our clinical results, which will be reported shortly, lend support to our theory.

More recently, we have had prepared capsules of sodium ricinoleate which we have employed in similar cases. It has been observed that some of our patients, after prolonged daily use of castor oil, tolerate doses of vaccine considerably larger than can be given usually, without reaction. Vaccines which produce marked local reaction may be detoxified by the addition of sodium ricinoleate (D.), so that little or no reaction follows intradermal injection. If



this reaction occurs in the test tube it is quite possible that dead bacteria in the intestines may be similarly detoxified, furnishing a local antigen, which may, in turn, aid in desensitization.

Clinically, it has been observed, in patients with evidence of allergy of intestinal origin, that there is, as a rule, very prompt relief of the feeling of distention and excessive gas formation, a lessening of fatiguability, a lessening or relief of pains in various parts of the body (headache, neuralgic pains in muscles, etc.). The palpitation, tachycardia and nervousness so frequently associated with excessive gas, are also relieved. Patients have commented on the fact that the stools have become less offensive after taking the ricinoleate. Some of our patients who have obtained marked subjective relief have complained of a recurrence of their symptoms when their supply of capsules became temporarily exhausted, with relief soon after resuming the medication. We have attempted to avoid psychic influences by not stating to patients the results we anticipate.

Our experience with this drug is too limited to enable us to state whether it has any effect on the bacterial flora or what its ultimate value may prove to be. We have given as many as six 5-grain capsules daily, though the majority of our patients have received only three daily. The drug appears to be entirely nontoxic in the doses employed; this was to be expected, as it is the sodium soap of castor oil.

Other possible therapeutic applications of this preparation are being investigated in our Clinic and will be reported at a later date.

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## THE OCCURRENCE OF POSITIVE WASSERMANN REACTIONS IN THE SPINAL FLUID OF TUBERCULOUS AND OTHER NONSYPHILITIC CASES OF MENINGITIS.

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THE earliest reference to this subject appears to be that of Zadek,<sup>1</sup> who, in 1918, reported 5 cases of meningitis in which the Wassermann reaction of the blood was negative, while that of the spinal fluid was positive. In 3 of the cases the offending organism was the meningococcus, in one the pneumococcus, and in one the tubercle bacillus. Syphilis was definitely excluded by autopsy as well as by history.

In January, 1927, Zange<sup>2</sup> summarized (in addition to those of Zadek) the reports of Kronfeld, Kraemers, Eicke, Lesser and Stern, each of whom had cited single cases with positive spinal fluid and negative blood in which there was absolute evidence against the occurrence of syphilitic infection. These were cases of epidemic or tuberculous meningitis. Zange further quoted the discussion of the matter by Plaut and Zalociecki who concluded that the results were due to errors of technique. Zange was unable to contradict these opinions, but reported from his own experience a number of cases in which the spinal fluid was negative, though there was evidence of meningeal irritation, clinically and by analysis, while the blood gave positive reactions.

Pilotti<sup>3</sup> presents a case with positive colloidal gold as well as Wassermann reaction in spinal fluid and blood in a formerluetie who had had specific treatment, the body of whom at autopsy showed no syphilitic lesions, but those of tuberculous meningitis. He cites similar observations by Hauptmann, Kafka, Assman and Eskuchen, as well as those of Plaut and Zalociecki, of cases of purulent meningitis following otitis media, epidemic meningitis and tuberculous meningitis, Plaut claiming that they were nonluetie meningitides in luetics. Pilotti further cites the reports of tuberculous meningitis and general carcinomatosis by Dungern and Helpert, cerebral neoplasm by Vincent and medullary tumor by Lowenburg, in which there were positive Wassermann reactions of the spinal fluid and negative Wassermann reactions in the blood. Histologically they were nonsyphilitic. He also mentions the presence of a positive reaction in the fluid in tropical sleeping sickness and in leprosy. Another Italian, Podesta<sup>4</sup> adds a case of "Negative Wassermann with positive cerebrospinal fluid findings."

Malcolm, of Vancouver<sup>5</sup> reports 8 atypical Wassermann reactions in a series of 848 spinal fluids, positive with the acetone insoluble antigen of Bordet and negative with the cholesterinized antigen of Kolmer, except in a case of cerebral tumor, which was positive with both antigens. In 3 cases, there were histories of syphilis while the remainder consisted of a case of bulbar paralysis, one of encephalitis lethargica, one of anterior poliomyelitis, one of tuberculous meningitis and the case of cerebral tumor mentioned. The blood reactions were not reported.

As the above reports are so few and scattered, the experience of the Dunn Memorial Clinic seems to warrant publication. Here it has been the custom for many years to make complement-fixation tests of the spinal fluid routinely in all cases of meningitis, in addition to the cell count, estimation of globulin and sugar and microscopic examination. Eight cases are presented from the files of the past five years, all definitely nonsyphilitic, in each of which there was a positive Wassermann reaction in the spinal fluid. The detailed analyses appear in the appended table.

SPINAL FLUIDS OF NONSYPHILITICS WITH STRONGLY POSITIVE  
WASSERMANN TESTS OF THE SPINAL FLUID.

	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Case 6.	Case 7.	Case 8.
Sex . . . . .	M.	F.	M.	M.	F.	M.	M.	M.
Cells . . . . .	86	33	..	100	..	400	..	186
Tubercle bacilli . . . . .	Few	..	+	..	Many	+	..	Few
Lymphocytes . . . . .	Many small	..	..	Many small	Many small	..	..	..
Globulin . . . . .	++	++	..	Slight	+	++++	++++	++++
Sugar . . . . .	++	+	..	30 mg. per 100 cc.	++	++	+	++
Wassermann reaction . . . . .	++++	++++	++++	++++	++++	++++	++++	++++
Mastic . . . . .	..	Comp. precip.	..	..	..	..	..	Mening. curve
Gold . . . . .	..	..	..	..	..	Mening. curve	Mening. curve	..
Blood Wassermann . . . . .	Neg.	Neg.	Neg.	Neg.	Neg.	..	..	Neg.
Clinical diagnosis . . . . .	Pul. tb.	Pul. tb.	Pul. tb.	..	..	..	Traum. mening.	Pul. tb.

It is noted that in Case 2 there was a complete precipitation by the mastic test. Case 8 showed a meningitis curve by this test, and Cases 6 and 7 by the colloidal-gold test. These additional tests are always made when there is sufficient fluid. Five of the fluids revealed the presence of tubercle bacilli, while Case 7 showed many intracellular diplococci. In the latter, the meningitis was the result of traumatism, in a child who had been struck by a motor-truck. This case and Case 6 were the only ones in which blood Wassermann tests were not made, as they were not seen until the time of the emergency (from the service of Dr. Wm. Pinckney Herbert). Cases 4 and 5 are of particular interest from the fact that Dr. J. LaBruce Ward, who referred them, took the pains to investigate the families and it was found that the blood of the parents and of the other children gave negative reactions, as well as that of the patients. In Case 3, the spinal puncture was made after death and the cells had disintegrated; similar conditions of the cells precluded counts in Cases 5 and 7. In the other cases the specimens were fresh. Cases 1, 2, 3 and 8 were adults who had advanced pulmonary tuberculosis, the others were young children. Case 6 was a negro. In none was there a history of venereal disease.

Naturally, the first question to arise is that of technique. The method which we have employed is that of Kolmer, with the single modification of incubating by means of the water bath instead of the ice box. This procedure has been necessary on account of the large number of patients referred for consultation from a distance, whose time for complete examination is limited, frequently to a one-night "stop-over." The method as modified, had the complete sanction of the late Dr. Dunn, who, early in his career, attained distinction in laboratory research, in which he continued to take an active interest

throughout his extensive clinical experience. In a personal communication, Dr. Kolmer says that he does not think he has ever observed a strongly positive Wassermann reaction in spinal fluids of cases of tuberculous and meningococcus meningitis, in nonsyphilitic individuals by his method, and states that "it is common for such fluid to be anticomplementary and that the controls are apt to hemolyze slowly, but may be completed in the period of secondary incubation and yet show some degree of inhibition of hemolysis in those tubes carrying antigen, due, presumably, to a summation of the effect of antigen alone and spinal fluid alone, upon complement." This opinion is based upon experience with his new method, in which he regards as very important the ice box primary incubation of eighteen hours at 6° to 8° C followed by ten minutes in a water bath at 38° C. It is his belief that the water-bath incubation may be much more likely to give falsely positive reactions. He discusses this matter in detail in his book "Serum Diagnosis by Complement Fixation."<sup>6</sup> In it he also observes that much less investigation has been devoted to the specificity of complement fixation in spinal fluid than in blood, but that his experience has covered the examination of fluids from all types of nonsyphilitic meningitis (pneumococcus, streptococcus, staphylococcus, meningococcus, tuberculous and influenzal, *with negative reactions in all*. (Italics his.) In textbook "The Cerebrospinal Fluid in Clinical Diagnosis," to our addition to this authority, Greenfield and Carmichael,<sup>8</sup> in their knowledge the most complete work on this subject in the English language, make the flat statement that "The Wassermann reaction is constantly negative with the heated fluid in cases uncomplicated by syphilis."

In rebuttal, it may be said that in one of the cases presented (Case 3) the Kolmer technique was followed throughout without modification. In an exigency, the analysis on the fluid of this patient, who had been under our care, was done in the laboratory of Dr. W. L. Grantham, who, incidentally, informs us that he has observed similar reactions in other cases. Further, if the results were due to an error in technique it would be reasonable to expect their frequent repetition, while the fact is that those submitted are exceptions in a long series of negative results. It is also noteworthy that in the cases under discussion all of the reactions were strongly positive (4+). Moreover, our technique has been thoroughly checked in many ways—first by Dr. Dunn personally, who was never too busy to visit the laboratory one or more times daily, and by means of other laboratories during the early incumbency of the serologist. Parallel tests by means of the colloidal-gold and mastic reactions over a period of years, and with the Meinicke test for several months, to say nothing of the Kahn procedure, have completely corroborated our Wassermann results. These have proved

acceptable to the Chief of the Clinic, Dr. Charles DeWitt Colby, who during the first eight of his seventeen years association with Dr. Dunn, was in charge of the laboratory, to which at that time the city, county and many physicians referred specimens of all kinds.

As for the previous experience of the serologist, it may not be amiss to say that he received his initial training in the Army Medical School in 1910, where at first the original Wassermann technique was used and later that of Colonel Charles F. Craig,<sup>9</sup> under whom he served at Fort Leavenworth, while that officer was becoming an outstanding figure in this field. He commonly performed as many as 100 Wassermann tests per week, and had an abundant experience with spinal fluids in consequence of the Army's policy to withhold discharge from the syphilitic register until the fluid, as well as the blood, was negative. During his connection of seven years with the Dunn Clinic he has averaged about 250 Wassermann tests per month.

If our results are assumed to be free from important technical error, our next consideration should be an explanation of their nature and possible causes. The coincidence of positive spinal fluid and negative blood serum seems to support the idea dwelt upon at considerable length by Pilotti and held by Wassermann, Plaut and Hauptmann, that the antibodies, which are responsible for the Wassermann reaction, are formed in the spinal fluid locally rather than permeating the membranes from the blood stream, as held by Zalociecki, Pilotti and others.

An original suggestion was offered by Dr. D. J. McCarthy, of Philadelphia, to whom an inquiry was addressed, as in addition to being a neuropsychiatrist, he has been associated with the Phipps Institute for many years, and has a rich background as a teacher and past president of the Philadelphia Pathological Society. He refers to "the autopsies at the Phipps Institute, which showed a very marked loss of cerebral substance both as to total weight of the brain and as to the evidence of atrophy of the frontal parietal area, such atrophy corresponding in a general way to the atrophic areas in paresis. The loss of brain substance was also shown in the very widely dilated ventricles." He offers this as a very possible explanation of the presence of the positive Wassermann reaction (presumably due to the increased lecithin and cholesterin) in the spinal fluid.

Another suggestion, which seems quite pertinent, has been advanced by Dr. Alfred Blumberg, pathologist to the Government Hospital at Oteen, to the effect that the reaction may be due to the increase in the number of cells in the fluid, in meningitis, which, by their fatty alcohol content, may change the surface tension sufficiently to cause the reaction.

Our own opinion is that the reaction may be due to the abundance

of microorganisms causing the inflammation, the mere presence of which, alone, may inhibit hemolysis, although it must be admitted that we have had other cases of meningitis with negative findings. In the future, we shall attempt to eliminate this factor by heating a portion of the fluid to the point of inactivation, even though Kolmer<sup>7</sup> believes this to be unnecessary with clear fluids kept at low temperatures and Craig warns against it. We shall also add an estimation of cholesterol to our routine examination, to determine the possible increase of that element from irritation of the meninges, as well as to the increased number of cells.

Finally, we regard the occurrence in these particular cases of the meningitic curve with the mastic and colloidal-gold tests (which is characteristic and quite different from the typical paretic curve), as significant of a process other than syphilis.

Of course, the last word has not been said as to the nature and specificity of the Wassermann reaction, and it is obvious that we have much to learn concerning the spinal fluid. It has long been recognized that it is not a specific complement-deviation test in the strict sense, as is shown by the efficiency of nonsyphilitic substances as antigens. It is curious that so little has appeared so far on the subject here presented, in the English language. It is hoped that more reports will be forthcoming in this country, and that some one may go farther into an explanation of the causative factors.

NOTE.—We desire to thank Dr. W. C. Brownson for the translation of the Italian literature; Dr. J. LaBruce Ward for assistance and inspiration, Dr. Alfred Blumberg for a survey of the German literature and Col. Percy M. Ashburn, of the Surgeon General's Library, for research and suggestions as to the bibliography.

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## CLINICAL OBSERVATIONS ON THE USE OF AN OVARIAN HORMONE: AMNIOTIN.

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CLINICAL studies of supposed hypofunction of the ovaries are seriously handicapped by the lack of an objective and mathematical index of ovarian activity. The situation is analogous to the observations made on hypothyroid syndromes before basal metabolic rates were measured. But both clinical and fundamental scientific profit accrued from the more or less empirical association of certain symptoms with deficiency of thyroid secretion. It must not be forgotten that even technically perfect basal metabolic measurements showing low rates do not in every case demonstrate a hypothyroidism. Clinical observation is just as necessary as before. The status of observations on the menopause, infantilism, amenorrhea and other menstrual irregularities is one of rather empirical grouping based on the history and physical findings. Lacking specific tests for ovarian activity in the human female, the clinician must make diagnoses that are probable rather than certain.

The conviction that the ovary produces a hormone has become a certainty with the demonstration by Allen and Doisy<sup>1</sup> of the active preparations from the Graafian follicle. With this material standardized biologically and shown to be the same in action for a variety of animal species, the clinician has a new means of investigating the disorders supposed to be due to hypoövarian function. It is frankly recognized that clinical results with such a hormone do not prove a syndrome due to lack of the hormone. When, however, the ovaries are known to be losing their activity as at the menopause, the symptoms common to this period may reasonably be supposed to result from a lack of ovarian secretion. If in such cases the administration of a hormone preparation gives definite relief from one or more symptom groups consistently, the probability of the association of cause and effect is greatly strengthened.

Such attempts to establish causative relations must be made with caution. Just as the use of thyroid preparations to hasten the reduction of obesity does not prove obesity always due to hypothyroidism, similar errors may be possible with ovarian hormones.

Furthermore, failure to secure results from use of the Graafian follicle preparations in treatment of symptoms thought to be due to ovarian hypofunction does not prove the diagnosis wrong. It is now recognized that there are at least two hormones obtained from the ovaries of animals. The possible complications are more than doubled by the presence of two hormones, follicular and luteal.

TABLE I.—RESULTS OF TREATMENT WITH AMNIOTIN.

Group.	Type of cases.	No. of cases.	Bene- fited.	Doubt- ful.	No relief.
1.	Menopause, with hot flushes and insomnia . . . . .	15	10	1	4
2.	Headaches with suspected menopause . . . . .	3	2	..	1
3.	Involutional psychosis . . . . .	3	..	..	3
4.	Angioneurotic edema, with amenorrhea . . . . .	2	1	..	1
5.	Infantile female type . . . . .	2	1	1	
	Totals . . . . .	25	14	2	9

With these possibilities in mind, we present a study of 25 cases that have been treated with amniotin. This is a preparation of the Allen and Doisy hormone secured from amniotic liquor of cattle. It is an aqueous solution, prepared for subcutaneous injection, in a concentration of 10 rat units per cubic centimeter. This material was supplied to us by the laboratory of E. R. Squibb & Sons. The standardization has been checked for us in the laboratory of Dr. F. L. Hisaw of this University. In several of these cases where subcutaneous injections had been followed by therapeutic relief we tried the use of vaginal pessaries of amniotin. These were prepared in glycerinated gelatin, containing 10 units per gram. They were furnished likewise by the Squibb laboratory.

The diagnostic grouping of our cases is indicated in the table of results. In Group 1 we have placed those women who had ceased menstruating or who were reporting the irregularity of menses which often precedes the menopause. In these cases the "hot flashes" in the skin of the face and neck, insomnia, variable increase in blood pressure, and frequent headaches are common symptoms. Obesity occurs frequently. Group 2 is different in that hot flashes were not reported. A menopause was suspected because of menstrual changes, accompanying or preceding the headaches. Group 3 represents an association of a known menopause within the few years preceding the gradual development of mental depression, melancholia, a sense of general inadequacy, and idea of reference. The menopause is assumed by some clinicians to be at least a factor in causing this psychosis. Group 4 is merely an empirical association of angioneurotic edema with ovarian disturbance because amenorrhea or the menopause occurred at about the time the attacks of edema first appeared. In Group 5 we attempt to include



only those female infantile cases in which there is no apparent involvement of the thyroid or pituitary glands.

We have made no attempt here to carry out systematic comparisons of the results from this treatment with those secured in our experience by the use of the other preparations of the ovary and corpus luteum. We have, of course, seen cases that were benefited by those other preparations. We have studiously omitted medication with depressants such as bromids or barbital and its analogues. Recognizing the frequency with which the vasomotor phenomena of the menopause may spontaneously and suddenly subside, we were prepared to see some results with any preparation tried. We feel, however, that the way in which immediate relief from hot flashes has followed on the days when amniotin was given, to return equally promptly when it was omitted, makes spontaneous improvement in so many cases entirely improbable.

A few case summaries follow. Successful issue of the treatment need not be described in detail except where particular features may be of interest in showing the unusual factors in the clinical course. The failures are mentioned in sufficient detail to show that failure might have been predicted.

**Group 1. CASE I.**—Mrs. D., aged fifty-eight years, complained of nervousness, insomnia, hot flashes eight to ten times daily, and pelvic pain. Physical examination showed nothing unusual. Some menopausal symptoms had been present for eight years. The use of 10 units of amniotin daily gave immediate relief. On the evening of the second day, six hours after the injection, there was an unusually severe flash, accompanied by peculiar abdominal symptoms and urinary urgency for six hours. Reduction of the dose to 5 units daily was followed by the return of an occasional flash. Insomnia was relieved at once. Transfer to the use of pessaries containing about 8 units each, inserted on alternate nights, again gave complete relief. Use of the pessaries on every third night was not quite adequate to prevent hot flashes. After several weeks, relief from hot flashes required the use of 10-unit pessaries daily, and still later the return to the use of 15 to 30 units hypodermically. Ten units hypodermically were no more effective at this time than when given by vaginal route.

**CASE II.**—Mrs. N., aged forty-three years, complained of obesity, insomnia, and hot flashes. Menses had continued after unilateral ovariectomy in 1925. First evidence of menopausal symptoms appeared in 1926. Hot flashes were irregular in occurrence, but few days passed without them. Ovarian tablets had given partial relief. Use of 10-unit doses of amniotin daily gave complete relief from the flashes and insomnia. Transfer to the use of 10-unit pessaries was made after only a few days because of pain from the use of the hypodermic (not after, but during the injection). Relief was not as complete until the pessary was retained by the use of wool tampons inserted into the vagina and allowed to remain overnight.

**CASE III.**—Mrs. O., aged thirty-one years, was convalescent from cholecystectomy and complained of irregular and profuse menstruation with very frequent hot flashes, for about one year. There was a marked hysterical history. Use of 10 units of amniotin daily gave marked relief from flashes

and general improvement in the sense of well being. An interval of forty-eight hours without treatment was followed by flashes eight to nine times daily. A 50-unit pessary was then used. She experienced an extreme chill, sweat and discomfort for over twenty-four hours, but was free from flashes for about forty-eight hours. Trials of smaller doses showed that, except for times of unusual nervous excitement the use of 12.5-unit pessaries was required about once in forty-eight hours to completely prevent hot flashes.

CASE IV.—Mrs. W., aged twenty-eight years, was admitted for treatment of diabetes mellitus. She was also severely anemic, as the result of bleeding hemorrhoids, had acute colitis and a history of bilateral ovariectomy and salpingectomy for gonorrheal infection. The rather peculiar subjective hot and cold feelings were at first thought to be due to insulin reactions, but this was conclusively disproved. Follicular hormone was used, 10 units daily for nine days, with some improvement. Lutein by mouth after that continued to give some relief. This case is recorded as doubtful.

Four patients who received no relief included an obese woman with cholecystitis, who left the hospital on the third day of the trial; a woman who had only objective manifestations of the flashes, and kept no record of the result of treatment since there was no subjective improvement in her long-standing spastic colitis which was her chief complaint at the time; and a woman whose menses were beginning to change in type, but who was considered to be essentially thyrotoxic. In the fourth case, hot flashes were only one of many complaints for which surgical intervention had been tried repeatedly, but in vain.

It is apparent that in 10 of the 15 cases found in this group results were satisfactory. These patients have been glad to continue the treatment. In the other 5 cases, success was hardly to be expected in at least 4. Success in two-thirds of these cases really understates the facts.

Group 2. Among the 3 cases of headache probably associated with the menopause, the success was not so definite as with the hot flashes. Two were, however, well pleased.

CASE V.—Miss G., aged forty years, was a severe asthmatic, with pulmonic artery enlargement and a retrosternal thyroid. Headaches occurred daily during periods of amenorrhea, which has been frequent for six years. Lutein hypodermically gave partial relief, but this relief was definitely greater with the use of 10 units daily of amniotin. Similar relief was procured during a second period of amenorrhea. Headaches never occur when menses are regular.

CASE VI.—Miss B., aged thirty-eight years, found similarly more uniform relief from headaches and asthenia with amniotin than with lutein.

CASE VII.—Mrs. L., aged thirty-four years, had numerous complaints, and was considered hysterical. Hysterectomy had been done fourteen years before. Headaches were particularly disconcerting. Use of 10 units of amniotin daily for five days, then 10 units twice daily for four days, gave no relief. The basal metabolic rate was from 13 to 23 per cent below the Du Bois normal prediction. The use of thyroid medication to elevate the

rate gave slight improvement. Successful issue to the amniotin therapy could hardly be expected.

**Group 3.** The three cases of involutinal psychosis studied have shown no benefit. One had 10 units daily for five days, the others had similar doses for periods up to three weeks. In one case there was possibly temporary improvement. This field may require more prolonged use of the amniotin, or probably a different type of substitution therapy.

**Group 4.** One of the two cases of angioneurotic edema observed was found to be complicated by a low basal metabolic rate. There was no improvement in the edema or the amenorrhea, of seven years' duration, by the use of amniotin.

**CASE VIII.**—Mrs. F., aged twenty-eight years, had a partial hysterectomy and ovariectomy in May, 1927. Angioneurotic edema appeared a year later. The attacks seem to be worse in periods of about one month. Treatment before we saw this patient had included soda, mineral oil, dietary restrictions, calcium salts, thyroid, nasal treatment, ovarian tablets, bromids, belladonna and morphin, as well as epinephrin in attacks. None of these had given any real relief. Over a period of three months with varying doses of amniotin it has been apparent that the edema attacks are greatly limited in frequency and intensity by doses of 10 units daily. The use of the 10-unit pessaries of amniotin is of service. The melting of the gelatin led to sufficient vaginal drainage and loss of material, even at night, so that the use of wool tampons was found necessary. This improved the results. After a few weeks this patient reported personality changes which are usually interpreted as a return of more normal secondary sex characteristics.

**Group 5.** The treatment of 2 cases of amenorrhea with incomplete development of female characters presents a most interesting test of the hormone value of amniotin. Only 2 such young women have been treated in the course of the eight months' use of amniotin. One of these shows questionable benefit from the treatment; the other very gratifying and positive development.

**CASE IX.**—Miss G., aged twenty-eight years, had been observed during three different periods of hospitalization, with such tentative diagnoses as hyperthyroidism, neurocirculatory asthenia, and polyglandular dyscrasia. In October, 1928, it was observed that the hair distribution was masculine in type, although concealed by shaving, the breasts were undeveloped, the hymen almost imperforate, the external genitalia infantile. Menses had begun at fourteen years of age, but had been irregular, with scanty flow. The interval had become about three months. The basal metabolic rate, which had been +5 and +17 per cent (Du Bois standard) on previous observations, was now 15 per cent below the same standard. Ten units of amniotin were given daily, beginning October 25. After five weeks there was a report of definite increase in appetite and weight. The hymen was incised at this time. Pelvic examination showed the internal genitalia to be of normal development. Two weeks later the patient reported that she was making subjective improvement. She had just experienced sensations in her right side which usually had been prodromal of menstruation. No flow had been seen for five months. The basal rate was now 11 per cent

below the standard. Amniotin was given in 12.5-unit pessaries daily for two weeks.

On December 28, after nine weeks of amniotin therapy, she reported consistent gain in weight and sense of well being. Amniotin was stopped, unfortunately, and thyroid given daily, in 1-grain doses. Two weeks later the basal rate had come up to the standard, the patient said she felt better than for many months, and menstruation appeared in more profuse flow than usual for her. Unfortunately for the experiment, it is not possible to evaluate either the thyroid or follicular hormone part of this therapy. The patient later reported that she was not feeling as well after two more weeks on thyroid alone. The thyroid was stopped, shortly before the expected next menstrual flow, but no menstruation occurred. Resumption of the use of amniotin was followed by the appearance of a delayed flow about five weeks later. We are tempted to attribute much of the progress to the amniotin, although the case must be recorded as doubtful at best.

CASE X.—Miss S., aged twenty-three years, was admitted to the neurological service for what proved to be a hysterical fracture of the left elbow. She had several hysterical episodes in her history. No menstrual flow had ever been seen. Breasts and genitalia were infantile. Amniotin was given in doses of 10 units daily for several weeks. After return to her home the patient continued the use of the injections, but was at times irregular. For a time the dose was 5 units twice daily, then 5 units daily and then was omitted for ten days out of each month. The first symptom reported was tingling in both breasts. This was present from the first week of the treatment and persists. By the end of a month there was notable increase in hair growth in the axillæ and at the pubic line, and the mammæ were developing. On readmission to the hospital after ten weeks' treatment there was a gain of 15 pounds, further hair and mammary growth, and the patient had developed a peculiar shy attitude toward male members of the staff—apparently an exaggerated sex consciousness. Her conversation showed that she was experiencing personality changes similar to those of an adolescent girl.

Beginning five months after the treatment started and recurring at four-week intervals the next two months she reported a slight papular rash followed after three days by nausea, and then after three to four days by cramplike pelvic pain. At the time of the third recurrence she was again in the hospital and the pelvic pain was followed by dark yellow vaginal flow, the first she had ever experienced. The nausea, pelvic pain and pelvic tenderness continued for over a week, manifestly being hysterically exaggerated. The same gynecologist who had made previous examinations reported a development of genitalia and of mammary tissue and hair which was quite surprising.

Although the subjective manifestations must be somewhat discounted because of the hysterical tendency here, the objective development and the personality change have given ample evidence that the amniotin has accomplished real feminization in this patient.

**Discussion.** It appears to us from this series of cases that amniotin possesses the activity for the human female which the animal experiments of Allen and Doisy would lead us to predict. In the hot flashes, insomnia, nervous instability, and headaches attributable to the menopause, artificial or spontaneous, amniotin has given very satisfactory relief. The improvement in angioneurotic edema associated with partial menopause confirms this point of view.

Most convincing of all is the development of an infantile type under the administration of the preparation.

The manufacturers of this preparation, as well as others, have recommended the use of much larger doses than we have employed. For the menopausal symptoms, we feel that doses of about 10 units daily are adequate, and may occasionally be excessive. A dose of 50 units was definitely too large.

The activity of amniotin in the form of vaginal pessaries was demonstrated on spayed monkeys in the laboratories of E. R. Squibb & Sons. We are convinced that the same result may be obtained in women. There are two difficulties to be encountered. One is that unmarried women are apt to object to this method. The other is that except with very firm closure of the vaginal sphincter there is sufficient drainage after the melting of the gelatin to occasion discomfort and loss of material. This is preventable by the use of wool or cotton vaginal tampons. Absorption from vaginal mucosa evidently goes on rapidly enough to allow of the use of a pessary retained overnight.

The occasion for the use of pessaries is the avoidance of the need of a hypodermic. Pessaries were used successfully in 7 of these cases. There has been no pain incident to the injection of amniotin in liquid form other than that occasioned by any hypodermic medication. Neither have we seen any evidence of serum reactions or hypersensitization phenomena.

Evaluation of this new material in comparison with the many older ovarian preparations is difficult at present. In contrast to the usual expectation based on experience with ovarian material by mouth, amniotin shows its activity at once in the cases of hot flash, insomnia, and nervous instability. It requires use at intervals of not over seventy-two hours, excepting in one case observed near the end of menopausal difficulty. This is to be correlated with the presence of the hormone in urine, indicating its rapid excretion. Since some of our patients have experienced relief from the use of lutein, we are inclined to believe that the commercial preparations of luteal material have been active largely because of their content of the follicular material. This is confirmed by the recent work of Hisaw.<sup>2</sup>

**Summary.** The effect of amniotin, an ovarian hormone secured from the amniotic liquor of cattle, has been studied on 25 women with menopausal and menstrual disturbances. Its use has been of marked value in the relief of the vasomotor phenomena of the menopause, and in promoting feminine development of one woman of infantile type.

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THE CURATIVE AND POSSIBLY SPECIFIC EFFECT UPON COLDS  
OF VACCINES CONSISTING OF THE STREPTOCOCCI  
PREVALENT DURING THAT PERIOD.\*

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In a recent paper<sup>1</sup> evidence was presented that vaccines, consisting of the more prevalent types of streptococci during a certain period, prevented colds during that period to a considerable degree. The present paper concerns more especially the relief or cure of acute colds by vaccines consisting of the varieties of streptococci that were most prevalent during the periods when the colds occurred, and in many instances a specificity among the streptococci, that seemed to cure, is demonstrated.

In this paper are presented as many of those patients, as it was possible to study, who were presented and mentioned in the former paper<sup>1</sup> and had had incomplete relief from colds following the preventive treatment. Since the patients presented themselves as soon as they were sure that they had a cold and not later than forty-eight hours after the onset of the symptoms, it was possible to use a vaccine for its curative effect. The result and type of vaccine used seemed to offer an explanation why the preventive inoculations had not been entirely successful and to demonstrate in some instances a selectivity or specificity among the streptococci in addition to the curative effect. Another group of patients who were repeatedly treated for acute colds are presented to show the curative value and in some instances a selectivity or specificity of the streptococcus group. The majority of these patients had not been given the preventive inoculations but were treated only when they had a cold. Some, however, had had preventive inoculations but many months had elapsed between the preventive inoculations and the next cold, and a few patients had had incomplete relief from the preventive inoculations.

In Table I will be considered 19 of the 97 patients who were presented in the tables of the former paper;<sup>1</sup> these 19 patients will be reproduced from the former paper. The first 10 patients were in Table II, the next 3 were in Table III and the last 6 patients were in Table IV. In Table II will be considered 20 of the 87 patients who were mentioned in the discussions of the tables in the former paper<sup>1</sup> but were not included in the tables because some received irregular and infrequent treatment, and others were given an autogenous

\* All of the patients were treated in private practice. The laboratory work was done with June Adkinson in the Medical Laboratory of the Peter Bent Brigham Hospital, Boston, Mass.

vaccine at times. In Table III are presented 15 patients who were repeatedly treated for acute colds.

As a rule, the patient presenting himself for treatment for an acute cold was given an initial dose, which was 3 minims, or 0.2 cc., of the mixed streptococcus vaccine, which comprised the more prevalent varieties of streptococci at that time and which were being used as a preventive at that time. Some patients, who had been given the preventive vaccine from which one of the most prevalent varieties of streptococci had been left out, either purposely or unknowingly at the time, were given a vaccine of only the one variety of streptococcus which was omitted in the preventive course of treatment and which was prevalent enough to have been given and ought to have been included in the mixed preventive vaccine. This experiment was tried with a few cases in 1925 with the *Streptococcus subacidus*, in 1926 with the *Streptococcus hemolyticus* Type I and in 1927 with *Streptococcus salivarius*. Of the patients with whom this was done all had had a cold from two to six weeks after the completion of the preventive vaccine from which the particular variety of streptococcus was omitted, so that it was possible to assume that that particular variety of prevalent streptococcus was probably the cause of the cold and since usually prompt relief followed the use of it as a vaccine this would seem to show specificity among the varieties of streptococci as to the cause and cure of some colds.

For the relief or cure of acute colds the vaccine offers the best and most prompt result, as a rule, if given between twenty-four and forty-eight hours after the onset of a definite cold. When the vaccine is given during the first few hours after the onset of symptoms of a cold, often the patient will state that the cold was aborted and occasionally he will state that it was made worse. Naturally, neither observation may be correct because there is no way of determining whether there would have been a cold at all in the former and no way of telling the severity in the latter case. Since for a short period following a dose of vaccine the resistance of the individual is supposed to be temporarily lowered and since the resistance is naturally already lowered at the onset of a cold, these are sufficient reasons to delay the use of the vaccine until the second twenty-four hours of cold symptoms and then the resultant effect of the vaccine is more evident. Most of the patients in this paper were treated between twenty and thirty-six hours after the onset of cold symptoms. Many experienced prompt relief, that is, they were either relieved or greatly improved on the day following the dose of vaccine. If they were only improved on the first day following the use of the vaccine, they had to be either relieved or practically free from the cold symptoms on the second or third day at the latest in order to be considered as prompt relief. In other words, there must be at least marked benefit during the first day

following the use of the vaccine and the benefit must rapidly increase during the succeeding two days so that the patient is well within three days after the treatment.

If, during the preventive course of inoculations, a patient has a cold at the time for the next succeeding dose of vaccine, the dose of the preventive vaccine should not be increased but instead the previous dose should be repeated and at the next regular visit the dose may be increased according to the regular schedule. An increase of the dose of the vaccine over the previous dose when the patient has an acute cold is usually followed by more severe symptoms; the explanation already given in the previous paragraph probably holds true. If, however, during the preventive course of treatment the patient develops a cold between inoculations but the acuteness of the cold has markedly subsided, the usual increase in the dose of the vaccine may be given. For further information concerning the administration of the preventive vaccine the previous paper<sup>1</sup> may be consulted.

The previous paper<sup>1</sup> details the composition of the mixed streptococcus vaccine which was used in this paper during the various years and the method of its administration. Before considering the first two tables, however, it might be well to explain the various symbols. The first column carries a number which represents a patient; in the second column the capital letter C means that the patient was under twelve years of age, and a blank means an adult; in the third column a capital letter C means that the patient was subject only to colds, a capital letter A means that the patient had asthma associated only with colds. The remainder of each table consists of groups of three columns; in the first column of each group is noted the year in which treatment was given, in the second column the result and in the third column the period of time in months between courses of vaccine. In the second or result column of each group certain symbols need to be explained. The capital letter W means that the patient considered himself well so far as colds or colds and asthma were concerned, the letter N means that the patient was well until "now" or very recently prior to the next course of vaccine or was well for the number of months indicated in the preceeding column. The symbols 1c mean that the patient had one cold during that interval and 1a means one attack of asthma. The letters SC mean slight colds which were of slight consequence and in an asthmatic patient the colds did not cause asthma. The capital letters PF mean that the patient considered himself practically free from colds or asthma; although he may have had slight colds or asthma, yet in comparison to the years previous to treatment he considered himself to be very well.

In Table I, as already stated, are presented 19 patients that are reproduced from the preceding paper.<sup>1</sup> From Table II of the preceding paper,<sup>1</sup> there are ten patients who were designated by the



following numbers, 1, 3, 4, 6, 12, 17, 18, 24, 28 and 34. From Table III, 3 patients, Nos. 9, 18 and 19, and from Table IV, 6 patients, Nos. 5, 8, 10, 19, 21 and 24, are reproduced. All of these patients had had preventive treatment and were treated also at the time they had a cold and the result of treatment will tend to show that the vaccine had curative value and in some instances there seems to be demonstrated a specificity among the streptococci.

TABLE I.

No.	Old No.	C = child.	C = cold, A = asthma.	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†
1	Table 2 Pt. 1	C	C	21	1c	6	22	1c	12	24	3c	18	25	1c	12	26	1c	12	27	1R	TR
2	" 2 " 3	...	C	21	W	22	23	W	24	25	1c	13	26	W	12	27	1c	12			
3	" 2 " 4	...	A	21	N	4	21	N	5	22	2c	18	23	N	14	25	N	23	26	W	18
4	" 2 " 6	C	C	22	2c	16	23	W	14	25	W	11	26	W	12	27	W	18			
5	" 2 " 12	C	A	23	W	12	24	W	13	25	N	16	27	1c	12						
6	" 2 " 17	...	A	23	N	6	24	N	10	24	2c	24	26	1c	18						
7	" 2 " 18	...	A	23	W	6	24	1c	12	25	W	12	26	1c	18						
8	" 2 " 24	...	C	23	1c	12	24	W	12	25	W	12	P	F	since						
9	" 2 " 28	C	C	23	N	16	25	W	7	25	1c	30									
10	" 2 " 34	A	A	20	3c	24	22	N	60												
11	" 3 " 9	...	A	24	W	12	25	...	26	1c	12	27	1c	12							
12	" 3 " 18	C	C	24	PF	12	25	W	12	26	W	12	27								
13	" 3 " 19	C	C	24	W	12	25	W	12	26	PF	12	27								
14	" 4 " 5	C	A	25	N	9	26	N	9	27	1c	12									
15	" 4 " 8	...	C	25	W	9	26	W	13	27	W	12									
16	" 4 " 10	C	A	25	1c	12	26	N	14	27	1c	12									
17	" 4 " 19	C	A	25	1c	12	26	1c	12	27	1c	12									
18	" 4 " 21	...	C	25	W	12	26	W	12	27	1c	12									
19	" 4 " 24	C	C	25	2c	12	26	N	15	27	W	12									

\* 1c = one cold; W = well; N = well until now; PF = practically free.

† Months between courses of vaccines.

**Case Reports.** CASE 1.—The patient, a boy, was subject to frequently repeated colds which were associated with redness of the throat, catarrhal condition of the Eustachian tubes, and discharging ears and fever. After the first course of vaccine (in 1921) he had one cold which appeared four months after his previous preventive inoculation, he was given an initial dose of the mixed vaccine and the cold was relieved in two days without his other usual symptoms. After his second preventive course of vaccine (in 1922) he had one cold which appeared six months after treatment, since it was a severe cold, rather than to give the usual vaccine, an autogenous vaccine was used following which the cold rapidly subsided. After the third course of vaccine (in 1924) he had three colds, the first one came eleven months after the preventive course of vaccine and was so mild that no treatment was given, the second cold appeared four months later still and was relieved in two days after an initial dose of the mixed vaccine, the third cold appeared three months later still and like the former one was promptly relieved. Following the course of preventive vaccine in 1925, he had a cold eight days after the last dose. Since during the preceding

two months the hemolytic subacidus type of streptococcus was very prevalent, but was not present in the vaccine which the patient had been receiving, an initial dose of vaccine of this organism was given, following which the cold disappeared in two days and the patient was free from colds for the succeeding twelve months. After the 1926 course of vaccine, the patient had a cold inside of three weeks, at this time the hemolyticus Type I was prevalent and as it was not included in the preventive vaccine, an initial dose of it was given and the cold symptoms were rapidly relieved and he was free from colds for the remaining twelve months. In 1927 no preventive course of vaccine was given because the patient had been so free from colds during the previous two years. During this twelve-month period the patient had three colds. One of the colds was not relieved by an initial dose of the mixed vaccine and it disappeared only after two doses of an autogenous vaccine. Three weeks later another cold appeared and it was relieved in two days by an initial dose of the mixed vaccine.

This case illustrates many different points which this paper will attempt to bring out. Previous to preventive vaccine treatment and the year that the preventive treatment was omitted, the patient had several colds, some of which were quite severe, however, during each of three-year periods (1922, 1925 and 1926) that the preventive treatment was given the patient had only one cold and that not severe. The one cold that the patient had in 1921 and two of the colds he had in 1924 were relieved in two days by an initial dose of the mixed vaccine. Following the course of vaccine in 1924, the patient had three colds in eighteen months, the first one appeared eleven months after the preventive treatment and was too slight to require treatment, the next one appeared four months later still or fifteen months after the preventive treatment, therefore the result from preventive treatment was successful for over a year.

In 1925 and 1926 the patient had a cold eight and sixteen days, respectively, after the last dose of preventive vaccine. Since many other patients had not had a cold following a course of the mixed vaccine and since this patient the previous year was free for eleven months, the logical assumption was that a bacterium other than those with which he had been treated was the cause of the cold. In 1925 the *Streptococcus hemolyticus subacidus* was prevalent at the time the patient had the cold, but it was not present in the preventive vaccine, therefore, the patient was given an initial dose of a vaccine consisting only of the subacidus variety and the cold subsided in two days. In 1926 the same reasoning was applied and the same procedure was followed with the exception that *Streptococcus hemolyticus* Type I was the particular organism involved, and prompt relief followed its use as a vaccine. Each of these two instances would seem to indicate specificity among the streptococci and lack of group polyvalent or nonspecific protection.

CASE 2 (Pt. No. 3).—Patient had a cold two months after the preventive course of vaccine was given in 1925, as did the previous case. Also, as in the previous case, since the preventive vaccine did not include hemolyticus subacidus and at the same time it was prevalent, this patient was given an initial dose of subacidus vaccine, following which cold was relieved on the second day. In 1927 this patient had a cold five weeks after the completion of the preventive course of vaccine which had contained all of the most prevalent types of streptococci, therefore, an initial dose of the mixed vaccine was given and the cold was relieved on the second day. Therefore, this patient would seem to illustrate in two instances the curability of streptococcus vaccine in acute colds and in the first instance there is more evidence in favor of specificity than of nonspecificity among the varieties of streptococci in the treatment of colds.

CASE 3 (Pt. No. 4).—The patient, following the preventive vaccine in 1922, had two colds, the first appeared nine months after the course of vaccine and it was rapidly relieved without asthmatic symptoms following an initial dose of the mixed vaccine. The second cold appeared eight months after the first cold or seventeen months after the preventive course of vaccine, and it was not benefited until after two doses of the mixed vaccine had been given with an interval of a week between them.

CASE 4 (Pt. No. 6).—A boy, aged nine years, who had had frequent colds in winter since the age of six years, two years previous to treatment had sinus infections with the colds, and in the spring previous to treatment he had a severe cold with myocarditis, two years previous to treatment his tonsils and adenoids had been removed. Following the preventive vaccine treatment in 1922 the patient had two colds, one which occurred ten months after the completion of the treatment lasted five days, but was not sufficiently severe for treatment, the other cold appeared thirteen months after the preventive treatment and it subsided on the second day after an initial dose of the mixed vaccine.

CASE 5 (Pt. No. 12).—A boy, aged five years, was subject to colds which were accompanied by asthmatic attacks. Following the preventive treatment in 1925 he was well for sixteen months, at the end of which time he began to have asthma, several increasing doses of the mixed vaccine resulted in no benefit. An autogenous sputum vaccine was prepared containing a pure culture of *Staphylococcus pyogenes aureus*, each treatment with this vaccine was followed by increasing benefit until there was relief after the third dose and the vaccine was stopped. The lack of benefit from the use of the mixed streptococcus vaccine and the rapidly progressive benefit during treatment with the *Staphylococcus pyogenes aureus* vaccine would indicate specificity among the bacteria in this case. In 1927, five months after a course of the preventive vaccine, the patient had a return of asthma and again an autogenous *Staphylococcus pyogenes aureus* vaccine relieved the condition.

CASE 6 (Pt. No. 17).—A man, aged fifty-four years, had been subject to head colds for ten years and to attacks of asthma which became so frequent that he was rarely free from it for more than two weeks, with the exception of the summer months. During the two-year period following the preventive vaccine in 1924, the patient had two colds, one appearing eight months and the other nineteen months after the preventive vaccine, in both instances following an initial dose of the mixed vaccine there was prompt relief from the cold in two days and no asthma developed. Following the preventive vaccine in 1926, the patient had two head colds, each of one day's duration, and sixteen months later he had a cold of several day's duration, from which he recovered two days after an initial dose of the mixed vaccine.

CASE 7 (Pt. No. 18).—A man, aged sixty-four years, had been subject to asthma chiefly with colds for the last three years with the exception of the summer months. In 1924, five months after the preventive vaccine treatment, the patient had more or less asthma which gradually disappeared while he was being given three doses of the mixed vaccine. In 1926, nine months after the preventive treatment, the patient had a cold and asthma, both of which rapidly improved following an initial dose of the vaccine.

CASE 8 (Pt. No. 24).—A middle-aged man, who was susceptible to colds, had a severe cold six months after the preventive treatment in 1923. The cold was not benefited by an initial dose of the mixed vaccine, but it rapidly

improved following an initial dose of an autogenous sputum vaccine which consisted of *Streptococcus nonhemolyticus fecalis*. Since an initial dose of the autogenous vaccine contained six times the quantity of *fecalis* that was present in an initial dose of the mixed vaccine, it is probable that the benefit which resulted was due to the larger amount of the causative bacterium, *fecalis*. Since the total quantity of bacteria was the same in both initial doses this would rule out nonspecificity at least and would tend to show specificity among the streptococcus varieties.

CASE 9 (Pt. No. 28).—A boy, aged eleven years, had been subject to frequent colds and bronchitis for two years with the exception of the summer period. Twenty months after his preventive course of treatment in 1925 he had a cold which was relieved on the day following an initial dose of the mixed vaccine.

CASE 10 (Pt. No. 34).—A middle-aged woman, a school teacher, had averaged five or more colds with asthmatic attacks for each of the last three years. During the two years following the preventive course of vaccine in 1920 she had three colds, four months, twelve months and sixteen months, respectively, after the course of vaccine was completed. In each of these three instances the cold was cured in two days without any asthma following an initial dose of the mixed vaccine.

CASE 11 (Pt. No. 9, Table III).—In 1925 the patient was given no preventive course of vaccine. During the twelve-month period he had five colds at irregular intervals and in each instance after an initial dose of the mixed vaccine the cold was relieved by the second day without asthma, which formerly was associated with colds. Two months after the preventive vaccine in 1926 the patient had a cold, and since the hemolytic Type I streptococcus was prevalent at this time and was not included in the preventive vaccine, he was given an initial dose of a vaccine consisting of this type of streptococcus, following which the cold was promptly relieved. Following the preventive vaccine in 1927 the patient had a cold which subsided in two days after an initial dose of the mixed vaccine.

CASES 12 and 13 (Pts. Nos. 18 and 19).—The patients, who are brothers whose ages in 1927 were eight and ten years respectively, had been given the preventive treatment three successive years with successful results, but in 1927 the preventive treatment was not given. During the succeeding twelve months each patient had three colds, with the former patient they were confined to the head and with the latter they were in the head and chest. In each instance rapid improvement to prompt relief within two to three days followed an initial dose of the mixed vaccine.

CASE 14 (Pt. No. 5).—A boy, aged four years, who had been very susceptible to colds followed by bronchitis for three years and during the last year had also had asthma. In 1925 and 1926 he was free from colds, bronchitis and asthma for nine months following the usual preventive course of vaccine. In 1927 he was given only five of the customary eight or nine preventive treatments and five weeks later he had a cold and asthma for two weeks before he was given treatment. The initial dose of the mixed vaccine was followed by improvement and a second dose a week later was followed by relief.

CASE 15 (Pt. No. 8).—A middle-aged woman who had for years been very susceptible to head colds accompanied by hoarseness and irritation of the throat. Following the completion of the preventive treatment in 1925,

1926 and 1927, she was free from colds, however, during the course of the treatment in 1927, after she had received seven doses of the vaccine, she did have a cold. It is to call attention to and emphasize this that the case is mentioned. Not infrequently do patients during the first two or three weeks of treatment have a cold, probably because sufficient resistance has not yet been developed. After six, seven or more doses of vaccine have been given, the patient sometimes has a cold, this may be due to lack of development of sufficient resistance or to temporarily diminished resistance which probably occurs during the twenty-four-hour period following the larger doses of vaccine. In the particular case at point the patient's sputum contained five varieties of streptococcus and four of these were present in the preventive vaccine, the other being an unusual one. This would seem to indicate that the preventive vaccine was not at fault. When the patient has a cold at the time a treatment is due, the dose of vaccine should not be increased, but instead the preceding dose should be repeated.

CASE 16 (Pt. No. 10).—A boy, aged twelve years, had had frequent attacks of asthma for several years and had always been very susceptible to head colds, he would be free from colds or asthma for only a few weeks at a time. Following the preventive vaccine in 1926 and 1927, he had a cold eight and six months, respectively, after completion of the vaccine treatment. In both instances an initial dose of the mixed vaccine was followed in two days by relief of the cold without any asthma.

CASE 17 (Pt. No. 19).—A boy, aged three and a half years, had since birth been very susceptible to head colds and during the last year he had had four attacks of asthma with colds, his adenoids had been removed at the age of two years without benefit. In 1925, two weeks after completion of the preventive vaccine he had a head cold from which he recovered in two days following an initial dose of the mixed vaccine. In 1926 he had a cold and asthmatic attack six months after the preventive vaccine, and he was not relieved until a second dose of the mixed vaccine was given. In 1927 he had one cold of two days' duration with very slight asthma.

CASE 18 (Pt. No. 21).—An adult male, had had frequent colds ever since he could remember. In 1927 six months after the preventive vaccine, he had a cold accompanied by aches and pains, sore throat, and general malaise which was called "grippe" by his local physician. After he had been ill for two days with these symptoms he was given an initial dose of the mixed vaccine which was followed two days later by relief.

CASE 19 (Pt. No. 24).—A boy, aged six years, had been subject to a head cold every three weeks with the exception of the summer period for several years. Following the preventive treatment in 1925 he had two head colds, one appearing two months and the other three months after the preventive treatment. The first cold was relieved on the day following an initial dose of *Streptococcus hemolyticus subacidus* which was given for reasons already mentioned in two previous instances and the second cold was relieved on the second day after an initial dose of the mixed vaccine.

In Table II are reported 14 of the 87 cases that were referred to in the previous paper<sup>1</sup> in the discussion of the tables but were not a part of the tables and, in addition, 6 other patients; namely, No. 4 and the last 5 in this table, that have not previously been mentioned.

TABLE II.

Number.	C = child. C = cold. A = asthma.	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†
Patient 1	A	21	3c	23	23	1c	10	24	2c	13	25	3c	24	27	2c	12
" 2	C	22	5c	36	25	2c	12	26	1c	12	27	W	12			
" 3	A	22	N	12	23	N	16	25	N	12	26	1c	12	27	W	12
" 4	A	23			24			25	sc	14	26	N	9	27		
" 5	A	20	N	9	21	N	9	22			27	W	12			
" 6	A	24	N	8	24	N	11	25	N	14	26	N	10	27	N	13
" 7	C	25	1c	12	26	2c	12	27	1c	12						
" 8	A	24	N	33	26	2c	12	27	2c	12						
" 9	A	22			23	N	28	25	W	30						
" 10	A	23			24	PF	30	27	1c	12						
" 11	A	20	N	22	22	N	24	24	N	24	26	N	21			
" 12	A	23	1a	20	25	PF	20									
" 13	C	25	2c	18	26	2c	24									
" 14	A	24	1c	13	26	W	12	27	no	tr.						
" 15	A	20	1c	12	21	1c	12									
" 16	C	25			26	W	18									
" 17	A	25	2c	36												
" 18	C	25	1c	24												
" 19	C	25	2c	24												
" 20	C	22	W	8												

† 1c = one cold; W = well; N = well until now; PF = practically free.

\* Months between courses of vaccines.

**Case Reports, Table II.** Patient No. 1 is a female aged fifty years, a school teacher who for fifteen years had been subject to frequent colds and bronchitis with some asthmatic attacks. When first seen in 1920, since she was having an attack of bronchitis and asthma, an autogenous sputum vaccine was given and after three treatments she became free from symptoms. In 1921 the preventive vaccine was given, following which she had three colds in the succeeding twenty-three months. The first cold appeared fourteen months after the preventive treatment and it was relieved three days after an initial dose of the mixed vaccine, with no bronchitis or asthma. The second cold appeared twenty months after the preventive treatment, and, like the former, subsided without other symptoms after an initial dose of the vaccine. After the third cold, which came three weeks later, another course of the preventive vaccine was given, as shown in the table, in 1923. Four months after this course of vaccine, which consisted of only five doses, a cold appeared and was relieved on the second day after an initial dose of the mixed vaccine. In 1924, following the vaccine, the patient had two slight colds which were evidenced chiefly by swollen nasal mucous membrane and sneezing. In addition to the usual mixed vaccine, an initial dose of *Staphylococcus pyogenes aureus* was given, following which in both instances all symptoms were relieved the next day. Following the preventive vaccine in 1925, the patient had three colds in the succeeding two-year period. The first cold appeared ten months, the second one fifteen months and the third one nineteen months after the preventive vaccine. Each cold was relieved within three days after an initial dose of the mixed vaccine without any associated bronchitis or

asthma. In 1927, two months after the preventive treatment, the patient had a cold which promptly cleared up following the initial dose of *Streptococcus nonhemolyticus salivarius*; this organism was given because it was prevalent at the time, but was not present in the preventive vaccine which the patient had been given.

Patient No. 2 is a female of middle age, a school teacher who had been subject to frequent colds for years. In the winter of 1921, during a period of six months, she had three colds, each of which was relieved in a day or two following a dose of the mixed vaccine. In 1922 she was given the preventive vaccine and during the succeeding three-year period she had only five colds. The first cold in 1922 appeared five months after the preventive treatment, and it was not relieved until she had been given three doses of the mixed vaccine. The second, third and fourth colds came one year, eighteen months and twenty-six months, respectively after the preventive vaccine, and each of them was relieved two days after an initial dose of the mixed vaccine. The fifth cold appeared two months after the previous one and did not disappear until after two doses of the vaccine had been given.

Patient No. 3 is a young man who for years had been subject to attacks of asthma at any time of the year. Following the preventive vaccine in 1922, he was free from asthma for a year, but at the end of this period he had an attack which promptly disappeared during the preventive treatment of 1923. After the 1923 course of vaccine, he was free from asthma for sixteen months, then he began to have slight asthmatic symptoms which were relieved by another course of preventive vaccine in 1925. Following the 1925 treatment, he was well for a year when he had a severe asthmatic attack and the vaccine again seemed to benefit. Two months after the preventive vaccine in 1926 he had a severe cold which his local physician diagnosed as "grippe," after this he was free from colds and asthma for ten months. In 1927, following the vaccine, he was well for a year. In this case it would seem that the vaccine had both curative and preventive value in the several instances that it was given, with the exception of the attack of grippe which it did not prevent. At this time it might be well to call attention to the following facts, namely, that some patients have had an attack of grippe in spite of the preventive vaccine, that some patients, who have had grippe several times before the vaccine was given, state that the vaccine has shortened the attack and made it much lighter than formerly, and that other patients think that the vaccine has prevented grippe.

Patient No. 4 is a young woman, aged twenty-eight years, who has been subject to frequent attacks of asthma at all times of the year since the age of one year. She was sensitive to wheat which was omitted from her diet. An autogenous sputum vaccine, which consisted of *Streptococcus mitis* and *salivarius*, was given, and for a year the patient was well with the exception that when she ate any wheat food she had asthma. The following winter the patient had four colds and asthma with each one; therefore, she was given the preventive vaccine in 1925 and during the succeeding fourteen months she had no asthma and only very slight colds. Following the vaccine in 1926 she was free from colds and practically free from asthma for nine months, then the asthma gradually returned and an autogenous sputum vaccine was given. This patient is presented to show the advisability of testing the patient for protein sensitivity and the necessity of avoiding any protein to which there is sensitivity and the importance of using autogenous vaccines in prolonged colds, bronchitis and asthmatic attacks before the anticold vaccine should be used.

Patient No. 5, a young man, had averaged four or five colds each winter for years and each cold was accompanied by asthma. Following the preventive vaccine in 1920 he was free from colds and asthma for nine months, at which time, in the month of August, both returned and another preventive course of vaccine was given (1921), after which the patient had no colds or asthma for a year, and then he had a severe cold and asthma, this was in the month of August, as was the previous cold and asthmatic attack. This time the preventive vaccine did not benefit, therefore, the patient was retested and found to be sensitive to ragweed pollen. Since the patient had had several attacks of asthma with constant bronchitis, an autogenous sputum vaccine was given and relief promptly followed the first few doses, the vaccine was a pure culture of *Streptococcus fecalis*. During the next two years the patient was given ragweed pollen treatment and was free from asthma, and for two years more without any treatment he remained well. In the fall of 1927 the patient again began to have colds and asthma, therefore, the preventive vaccine was given and for the succeeding year no colds or asthma developed.

This patient is similar to the former in that the importance of doing skin tests and of giving autogenous vaccines is evident, and, in addition, the necessity of giving pollen treatment when indicated. Since the mixed vaccine, which contained *Streptococcus fecalis* along with other varieties did not benefit, whereas a vaccine of *fecalis* alone did promptly relieve, this case would seem to illustrate specificity since the total quantity of both vaccines was alike, and the only difference was that in the same dosage there was six times the quantity of *fecalis* in the autogenous vaccine as compared to the mixed vaccine.

Patient No. 6, a woman, aged thirty-one years, had been subject to paroxysmal attacks of asthma for years with the exception of the summer period. In 1923, since she was having a prolonged attack of asthma with morning expectoration, she was given an autogenous sputum vaccine, for six doses, during which time she became well and remained so for three months when she had another attack of asthma. In 1924 she was given six doses of the preventive vaccine and during this time the patient was free from asthma and remained free for eight months. In the latter part of 1924 she was given another course of the mixed vaccine for six doses, with freedom from asthma for ten months. In 1925 there was freedom for fourteen months following a full course of the vaccine, in 1926 she was free for ten months and in 1927 she was free for thirteen months, furthermore, during each series of vaccine the patient rapidly became free from the asthma which she was having at the beginning of each course of treatment. Therefore, in this case, whereas following the autogenous vaccine the patient was free from an attack of asthma for only three months, following each of four courses of preventive vaccine, the patient was free for from eight to fourteen months and the vaccine seemed to relieve each attack as well as did the autogenous vaccine.

Patient No. 7 is a woman, aged fifty-one years, who had been subject to frequent colds and frequent attacks of grippe all her life. Following the preventive vaccine in 1925 she had one cold which appeared two weeks after the course of vaccine was completed. As with other patients already mentioned, *Streptococcus hemolyticus subacidus*, although prevalent was not present in the preventive vaccine which was given to her, she was given an initial dose of the subacidus vaccine following which she was much better and after a second dose there was relief in two days. Following the preventive vaccine, in 1926, the patient had two colds, one appeared five weeks and the other seven months after the vaccine. Following two



doses of *Streptococcus hemolyticus* Type I the first cold was relieved; this vaccine was given because this type of streptococcus was prevalent at the time but was not present in the preventive vaccine with which the patient was treated. Following the vaccine in 1927 the patient had two colds, the first one came five weeks and the other came six months after the completion of the treatment. A dose of the mixed vaccine did not benefit the first cold, but in three days relief followed the same quantity of a vaccine of *Streptococcus salivarius*; this was given because it was prevalent at the time but was purposely omitted from the patient's preventive vaccine. The second cold subsided on the second day after a dose of the mixed vaccine which contained the *salivarius* organism.

Therefore, in this case the frequency of colds, to which the patient was subject, was reduced by more than one-half and she had none of her usual gripe attacks. Two colds were relieved in two days following an initial dose of the mixed vaccine. One cold was not benefited by the mixed vaccine, but was promptly relieved following a dose of *Streptococcus salivarius*, and the other two colds seemed to be cured by doses of *Streptococcus subacidus* and *hemolyticus* Type I, respectively, these three instances would seem to illustrate specificity.

Patient No. 8, a girl, aged fifteen years, had been subject to frequent colds and attacks of asthma for years and some winters she would have an attack of asthma every one or two weeks. Following the preventive treatment in 1924 she was free from asthma for so long, namely three years, that in 1926 when she did have a cold and asthma only four preventive treatments were given rather than the usual eight or nine. Three months after this short series of preventive treatments she had a cold and asthmatic attack and eight months later she had a cold, in both instances prompt relief followed one dose of the mixed vaccine. In 1927 the patient was given the regular course of preventive treatment. During the treatment she had a cold, and from her sputum was isolated *Streptococcus infrequens* and *hemolyticus* Type I, two months later she had an attack of asthma which was relieved on the day following an initial dose of the mixed vaccine, and at this time her sputum contained *Streptococci infrequens*, *anginosus* and *ignavus*, all of which were present in the vaccine. One month later still she again had asthma which was not benefited by the mixed vaccine and, since her sputum contained only *Streptococcus infrequens*, she was given a dose of a vaccine containing only this organism, following which there was prompt relief on the next day. These instances would seem to indicate specificity among the varieties of streptococcus in the treatment of colds and asthma in this particular case.

Patient No. 9, a female, nurse, aged thirty-four years, had had frequent attacks of asthma for five years, she also had frequent colds and the asthma was worse with the colds. In 1922, since she was having a prolonged attack of asthma, she was given an autogenous sputum vaccine consisting of streptococci; while this vaccine was being prepared, however, she was given a dose of the mixed vaccine without benefit. Following one dose of the autogenous vaccine, there was definite improvement, this would seem to indicate a specificity among the streptococci. Since she was free from asthma after four doses of the autogenous vaccine she was then, in 1923, given the preventive vaccine, following which she was free from asthma and had no colds of any account for over two years. Since the last course of vaccine, in 1925, the patient has been free from colds and asthma.

Patient No. 10, a young woman, a telephone operator, had been subject to colds frequently for many years and during the last year she had had

attacks of asthma with colds. In 1924 she was given the preventive vaccine, following which, for the succeeding thirty months, she was practically free from colds and asthma, in that she had very slight attacks at infrequent intervals. In 1927 the preventive vaccine was given again and two weeks after its completion the patient had a grippe cold. A dose of the mixed vaccine did not benefit, but following a dose of an autogenous sputum vaccine the patient was relieved in two days. Since the autogenous vaccine contained *Streptococcus fecalis* and *equi*, this would seem to be another instance of specificity.

Patient No. 11, a middle-aged woman, had been subject each year to three or four attacks of asthma, always with a cold, for seventeen years, with the exception of one year when she was free following influenza. Following the preventive vaccine in 1920 she was free for nearly two years, when she had a cold and an attack of asthma from which she recovered in two days after the first dose of preventive treatment in 1922. After completion of the vaccine she had no more colds or asthma until 1924, when the vaccine again relieved her, but only three treatments were given at this time. In 1926 the patient returned with a cold and asthma and again an initial dose of the vaccine was followed by rapid relief; this time four doses were given and she remained free for twenty-one months, when she had another attack which was relieved in two days after one dose of the vaccine. This is the only case where so few preventive doses of the mixed vaccine were followed by long periods of freedom from colds and from asthma.

Patient No. 12, a middle-aged woman, for years had been subject to frequent colds and to a continuous wheeze, cough and expectoration. Because she was having continuous wheezing, cough and expectoration she was given an autogenous sputum vaccine, during the administration of which she became free from the chronic symptoms but she continued to have frequent colds. In 1925, four months after the completion of the autogenous vaccine, she was given the preventive vaccine and she was free from both colds and asthma for six months when she had a cold and a return of the cough, expectoration and wheezing. Again she was given an autogenous sputum vaccine, after a few doses of which she became well and remained so for one year. In 1925 the patient had a return of colds and asthma so that the preventive vaccine was again given. The patient stated four months later that she was very well, but was having slight wheezing at times with some expectoration. Again an autogenous vaccine was given, following which she was well for over a year and during the second year she had only slight colds and slight wheezing but no real colds or asthma. Although it is impossible to state what kind of vaccine gave the most relief, it is evident that desirable results followed in two separate instances when both kinds of vaccine were given, and in such cases, where there is evidence of chronicity, or incomplete relief from the mixed vaccine, an autogenous vaccine is indicated and the combination seems to give better results than either alone.

Patient No. 13, a middle-aged man, had been very susceptible to colds for years. In 1925 he was given the preventive vaccine and had no colds for nine months and the cold at that time was relieved in two days by an initial dose of the mixed vaccine. He had a second cold three months later, and this one also promptly disappeared following a dose of the mixed vaccine. In 1926, following the preventive vaccine, the patient had two colds in the succeeding two years. The first cold was sixteen months and the second one twenty months after completion of the preventive vaccine, and both were relieved on the second day after a dose of the mixed vaccine.

Patient No. 14, a girl, aged six years, had been subject to colds and asthma with colds since infancy. Following the preventive treatment in 1924 she was free from asthma and colds for eleven months, and the cold that she had at the end of this period was relieved without asthma after a dose of the mixed vaccine. Following the preventive treatment in 1926 she was free from colds and asthma for a year. During the next two years the preventive vaccine was not given and the patient had many colds and asthmatic attacks.

Patient No. 15, a young man, had been subject to four or five colds a year, and during the last two years he had had asthma with the colds. Following the preventive vaccine which was given in 1920 the patient had one cold, from which he recovered without asthma on the day following an initial dose of the mixed vaccine. Following the treatment in 1921 he had slight wheezing two months after the treatment, but on the day following a dose of the mixed vaccine he became free. In succeeding years the patient took the vaccine only when he had a cold; therefore, he is presented in Table III as Patient No. 1.

Patient No. 16, a girl, aged eight years, had been subject to colds, attacks of bronchitis, earache and frontal headache, accompanied by fever, for years. She had lived in Texas, Iowa, California and Massachusetts without benefit. Since she was having one of her usual attacks of bronchitis she was given, in 1925, four doses of an autogenous sputum vaccine, during which treatment she became well. The autogenous vaccine contained *Streptococcus infrequens*, hemolyticus Type III and nonhemolyticus Type III. Following the autogenous vaccine treatment, she was given in 1925 the preventive treatment and she had no more colds or other symptoms when she was last heard from, eighteen months later.

Patient No. 17, a girl, aged four years, had been subject to frequent and severe colds which during the previous two months had caused two attacks of asthma, and for the previous six months she had had a persistent cough and evening temperature of 100° F. She was given a course of the preventive vaccine, following which there was marked improvement and normal temperature. After an interval of two months the course of vaccine was repeated. She was free from colds and asthma for twenty months, then she had a cold and asthma for several days, but on the day following a dose of the mixed vaccine she was relieved. A year later she had another cold and asthma for two days and again she was relieved on the day following one dose of the mixed vaccine.

Patient No. 18, a boy, aged seven years, had had frequent colds with a chronic cough for two winters. Following the preventive treatment in 1925 he had a cold one year later that was cured on the second day after a dose of the mixed vaccine, and he did not have another cold for a second year, and even since then the colds have not been sufficiently serious to require treatment.

Patient No. 19, a boy, aged six years, the son of Patient No. 15, was susceptible to colds, and in 1925 he was given the preventive vaccine, following which he had two colds in the succeeding two-year period. These two colds came two and four months, respectively, after the completion of the mixed vaccine, and both were relieved on the day after an initial dose of *Streptococcus subacidus* vaccine which was given because this organism was very prevalent at the time, and it was not present in the preventive vaccine that was given to the patient.

Patient No. 20, a young woman, a school teacher, who was a sister to Patient No. 15, had been very susceptible to colds for years. In 1922 she was given the preventive vaccine, following which she had no colds for eight months. Beginning in 1923 she took the treatment only when she had cold, so that this patient is presented in Table III as Patient No. 2.

In Table III are presented 10 patients, who were treated for three years or more only when they had a cold and the treatment consisted of 3 minims or 0.2 cc. of the mixed vaccine which was composed of those varieties of streptococci which were most prevalent at that time; the bacterial count was approximately 100 million per minim.

TABLE III.—NUMBER OF COLDS PER YEAR IN PATIENTS RECEIVING VACCINE ONLY DURING COLDS (NO PROPHYLACTIC VACCINATION).

	1921.	1922.	1923.	1924.	1925.	1926.	1927.	1928.
Patient 1 . . . .	3	3	4	3	3	3	4	
" 2 . . . .	..	5	4	4	5	5		
" 3 . . . 1	1	1	1	4				
" 4 . . . .	1	1	1	1	1	1	1	1
" 5 . . . .	..	4	1	1	3	..	2	
" 6 . . . .	..	3	1	1	1	2		
" 7 . . . 2	..	2	4	3				
" 8 . . . .	..	4	4	4	4			
" 9 . . . .	..	..	1	2	3	1		
" 10 . . . .	..	..	..	..	3	3		

Patient No. 1 was presented in Table II (Pt. No. 15) as having had preventive vaccine treatment in 1920 and 1921 and the results of such treatment were discussed. During the years 1922 and 1928, inclusive, it is noted in Table III that this patient averaged to have three colds during each of the seven years or a total of twenty-three colds. In nineteen instances one dose of the mixed vaccine was followed by relief in two days and in the four other instances one dose resulted in benefit and a second dose one week later was followed by relief; in only one instance did asthma occur.

Patient No. 2 was presented in Table II (Pt. No. 20) as having had preventive treatment in 1922 only. During the years 1923 to 1927, inclusive, as noted in Table III, this patient had a total of twenty-three colds; she had four colds during each of two years and five colds during each of three years. In twenty-one instances prompt relief on the next day followed one dose of the vaccine and in the other two instances a second dose was given before complete relief was obtained.

Patient No. 3 is a young woman who has always been subject to frequent heavy colds and during the previous six years she had had asthma with colds. During the years 1921 to 1924, inclusive, the patient appeared for treatment only when she had a bad cold with asthma for two or three days. In three of the four instances there was relief on the first day following the mixed vaccine, and in the other instance benefit followed the first dose and relief followed a second dose of the vaccine a week later. In 1925 the patient appeared for treatment for four colds, and each time there was relief on the first or second day following one treatment with the vaccine.

Patient No. 4, a middle-aged man, was subject to one cold a year, and for seven successive years each cold was cured in one to three days following one dose of the mixed vaccine.

Patient No. 5, a middle-aged woman, had been subject to colds and asthma for ten years. In 1923 she was treated for four colds, two of the colds were not relieved until a second dose of the mixed vaccine was given, the other two colds subsided on the first or second day following one dose of the vaccine. In 1924 and 1925 she was treated for one cold each year, and each cold promptly subsided after one dose of the mixed vaccine. In 1926 she was treated for three colds, two of the colds were promptly relieved on the second day by one dose of the vaccine and the other one was not relieved until after a second dose. In 1928 she was treated for two colds and both times a second dose of the vaccine was given before she got relief. With all of the colds for which the patient was treated she also had asthma.

Patient No. 6 is similar to the former in that she presented herself for treatment only when she had asthma with her colds. In 1923 she had three colds with asthma and in each instance there was relief within three days after a dose of the mixed vaccine. During the next three years she was treated for one cold with asthma each year, and each time she was relieved by the second day after one dose of the vaccine. In 1927 she was treated for two colds with asthma and each time, as before, relief followed one dose of the vaccine.

Patient No. 7, a young man, had been subject to vasomotor rhinitis and frequent colds for years. During the years 1921 and 1923 the patient was treated for two colds each year, in three instances a second dose of the mixed vaccine was required before complete relief was realized, but in the other instances prompt relief followed one dose of the vaccine. In 1924 he was treated for four colds, two required two doses of the vaccine and the other two colds rapidly subsided after one dose of the vaccine.

Patient No. 8, a middle-aged man, who was subject to colds which occasionally went into his chest, was treated for four colds in each of the four years, 1923 to 1926, inclusive. Each year three of his colds were cured after one dose of the mixed vaccine, but each year one cold was not relieved until after a second dose of the vaccine was given.

Patient No. 9, a middle-aged woman, was subject to "asthma colds" for six years. In 1924 a dose of the vaccine was followed on the second day by relief. In 1925 one cold was relieved in a day or two after a dose of the mixed vaccine, for another cold in the head she was given a dose of *Staphylococcus pyogenes aureus* without benefit, and a week later, following a dose of the mixed vaccine, the cold was well in two days. In 1926 she was treated for three colds, from all of which there was recovery by the second day following one dose of the mixed vaccine without any symptoms of asthma. The following year the patient was treated for one cold which likewise promptly disappeared after one inoculation.

Patient No. 10, a young man who was subject to head colds, was treated for three colds in 1926 and three in 1927. Four of the six colds were relieved on the second day following one dose of the mixed vaccine, but the other two were not relieved until a second dose of vaccine five days later was given.

The following patients who have already been discussed might be included in this table, namely Patients 1, 2, 7, 8 and 13 who were

presented in Table II and Patient 1 in Table I. These 6 patients were treated for numerous colds and the results have already been mentioned in the discussion of the respective patients in Tables II and I.

During the years 1921 to 1925, inclusive, 42 patients other than any appearing in this paper were treated with the mixed vaccine one or two times when they had a cold. Ten of these patients were asthmatics and were treated once for a cold, 4 were asthmatics who were treated for two colds, 10 were hay fever patients and were treated once for a cold; 2 others were hay fever patients and were treated for two colds, 10 were normal cases who were treated for one cold and 6 others were normal cases who were treated for two colds. All of this group of 42 patients were relieved of their colds in from one to three days' time following one dose of the mixed vaccine.

**Summary.** *Table I.* In this Table are discussed 19 of 97 patients who were presented in a former paper<sup>1</sup> and who received preventive treatment for colds with vaccines consisting of the varieties of streptococci that were prevalent during the periods of treatment. This particular group of patients was selected for the present paper because they presented themselves for further treatment whenever they had a cold.

This group of patients was treated with mixed streptococcus vaccine, as described above, for a total of thirty-seven colds. Thirty-one of these acute colds rapidly and promptly subsided following an initial dose of the mixed vaccine and six colds were not benefited.

Two of the six colds that were not benefited by the mixed streptococcus vaccine promptly subsided following the same dose of an autogenous streptococcus vaccine; this would seem to illustrate specificity among the varieties of streptococci in the treatment of colds in these two instances.

Another definite case illustrating specificity is that of Patient 12, whose asthma on two different occasions was not benefited by the mixed streptococcus vaccine but both times there was rapid improvement following treatment with a vaccine of *Staphylococcus pyogenes aureus*.

Five other instances are of interest in that one of the prevailing varieties of streptococci was omitted from the preventive vaccine that was given and a cold which developed shortly afterward was promptly relieved following a dose of vaccine which contained only the omitted variety of streptococcus. These 5 instances concerned *Streptococcus subacidus* with Patients 1, 3 and 24 in 1925 and *Streptococcus hemolyticus* Type I with Patients 1 and 9 in 1926. Under the circumstances which prevailed in these 5 instances, the result would indicate specificity among the varieties of streptococci.

*Table II.* The twenty patients in this table had more or less preventive vaccine treatment. Fourteen of them were included in

the 87 referred to in the discussion of the previous paper<sup>1</sup> but were not included in the tables of that paper.

This group of patients was treated with the mixed streptococcus vaccines as described above for a total of forty colds. In 33 instances the cold promptly and rapidly subsided following an initial dose of the vaccine and in 7 instances the colds were not benefited.

Three of the seven colds that were not benefited by the mixed streptococcus vaccine promptly subsided following the same dose of an autogenous streptococcus vaccine; in one instance the autogenous sputum vaccine was *Streptococcus infrequens* alone, in another it consisted of *Streptococcus fecalis* and *equi* and in the third case the variety was not determined. These three instances would seem to illustrate specificity among the varieties of streptococci in the treatment of colds.

Five other instances are of interest in that one of the prevailing varieties of streptococci was omitted from the preventive vaccine that was given and a cold which developed shortly afterward was promptly relieved following a dose of vaccine which consisted only of the omitted variety of streptococcus. These 5 instances concerned *Streptococcus subacidus* with Patients 7 and 19 in 1925, *Streptococcus hemolyticus* Type I with Patient 7 in 1926 and *Streptococcus salivarius* with Patients 1 and 7 in 1927. Under the circumstances which prevailed in these 5 instances, the result would indicate specificity among the varieties of streptococcus in the treatment of colds.

*Table III.* In Table III are presented 10 patients who were not given the preventive vaccine treatment but were treated with the mixed streptococcus vaccines only when they had a cold. This group was treated for a total of one hundred and twenty colds. In 96 instances prompt relief followed one dose of the vaccine but in the remaining 24 instances the patients returned a week later for a second inoculation; therefore, these 24 instances may be called failures from the curative standpoint. Forty-two other patients were treated for a total of fifty-two colds during the period 1921 to 1926 inclusive with prompt relief.

**Conclusions.** A vaccine consisting of the varieties of streptococci that are most prevalent at certain periods seems to be beneficial in the relief or cure of acute colds that occur during that period.

The same vaccine used as a preventive was not always successful, probably because in many instances a cold or asthmatic attack which followed its use seemed to be due to a variety of streptococcus not present in the vaccine.

No attempt was made to prove specificity among the varieties of streptococci; nevertheless, in numerous instances specificity seemed to be quite evident.

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## SOME EXPERIMENTS IN INTRACRANIAL PRESSURE IN MAN DURING SLEEP AND UNDER CERTAIN OTHER CONDITIONS.

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Mosso, in 1881, wrote a treatise on "The Circulation of the Blood in the Brain of Man." In this book, he attempts to show that sleep is associated with a decrease in the intracranial pressure which he thought was due to a cerebral anemia. His work is based on experiments on three patients and the tracings illustrating his theory seem to cover too short a period to be convincing. His apparatus resembled our own, but was somewhat more complicated and not so sensitive for, obviously, it did not always record falls in the intracranial pressure (see page 137, Fig. 53).

Since Mosso's time, the anemic theory of sleep has been a popular one with physiologists. This theory has been supported by such workers as Tarchanoff, Villemin, Hill and Howell. On the other hand, there have been workers who have taken the view that sleep was caused by cerebral congestion—among these are Kennedy (1877), Langlit, Regard, Czerny and Shepard. There are other, perhaps less popular, theories or at least partial explanations of sleep among which may be mentioned the neuronc theory of Cajal and Duval. The number of these theories and the prevalence of the anemic theory of sleep seem to depend on the lack of direct observation or experiment upon the brain itself during sleep. Howell, for example, assumes that, since the bloodvessels of the extremities are dilated during sleep (as he has shown by plethysmographic experiments), the bloodvessels of the brain must be relatively empty.

Some years ago, on the service of Dr. Foster Kennedy at Bellevue Hospital, we had the opportunity of making direct observations on 2 cases of brain hernia during sleep. During the past year we have studied 2 more cases on the same service. In a fifth case we have studied Jacksonian epilepsy in a patient with a brain hernia. In 2 of these cases we have made observations on the intracranial pressure under various other conditions. These 2 cases had a



subtemporal decompression with a cerebral hernia over which the dura had been cut and left unsutured.

We have obtained 19 tracings taken during sleep; 13 were made during natural sleep and 6 while the patients were under the influence of hypnotics. These all show that the intracranial pressure rises as the patient falls asleep—this increase of pressure being maintained during sleep—and falls again to its normal level when the patient awakes. In our cases the process of falling asleep was a gradual one, the intracranial pressure rising slowly for a matter of ten minutes before the patient was sound asleep and before the curve reached its highest level. On the other hand, awakening is effected in a shorter time and is accompanied by a more sudden change of the pressure.

In some of the tracings obtained under ideal conditions, where the patient was aroused and again fell asleep, we have found a rhythmic fluctuation in the upward tendency of the curve as the patient falls asleep. We feel that this has some significance in the theory of sleep which we propose.

Two of us have made observations on the fundus oculi during sleep, while the patients were under the influence of paraldehyde, the pupils having previously been dilated with homatropin. No change in color of the fundus or in size of the retinal vessels could be seen as compared with their appearance while awake.

During sound sleep, the respirometer shows the thoracic breathing to be much deeper than when the patient is awake.

Howell's plethysmograph tracings of the arm (*Text Book of Physiology*, page 266) have a remarkable resemblance to our tracings obtained from the brain during sleep. We believe that the change in volume shown in these two series of tracings is attributable to the same phenomenon, namely, increase and decrease of blood volume.

Figure 1 illustrates the apparatus, which consists of a closed air tambour system under a positive pressure of about 12 mm. of mercury. One tambour was strapped and bandaged over the brain hernia. The other was attached to a light-weight pointer, which registered on a smoked drum the changes of intracranial pressure due to pulse, breathing, sleep and the other conditions we are about to describe. The drum was regulated so that it made a complete revolution in twenty minutes. At times the drum was stopped so as to allow observation over a longer period of time. In most cases our tracings represent one complete revolution of the drum, although they have not all been photographed to the same scale. In some cases a clear photographic reproduction could not be obtained, so that it was necessary to trace these on paper placed over the original. This tracing was then easily photographed.

Figures 7, 8 and 9 demonstrate the lowering of the intracranial pressure in one of our patients on being aroused.

Figures 10, 11 and 12 are similar tracings on another patient. In Figure 11, a pneumographic tracing was made at the same time.

Figure 15 shows scalp control.

Figure 16 shows a sleep curve (Brady) while the patient was sitting in a chair. After he was aroused fully he was given an inhalation of 5 minims of amyl nitrite. Later jugular compression was applied for periods of ten seconds. Note here that the fall in intracranial pressure on awakening is much greater than in the tracings taken when the patient was lying down.

Figure 18 shows a marked sudden rise of intracranial pressure during the inhalation of 5 minims of amyl nitrite and for about one minute after the inhalation was stopped. The pressure then fell rather rapidly. During the rise in the curve the blood pressure dropped from 94 systolic, 60 diastolic to 80 systolic, 48 diastolic. By the time the intracranial pressure had returned to normal the blood pressure was normal.

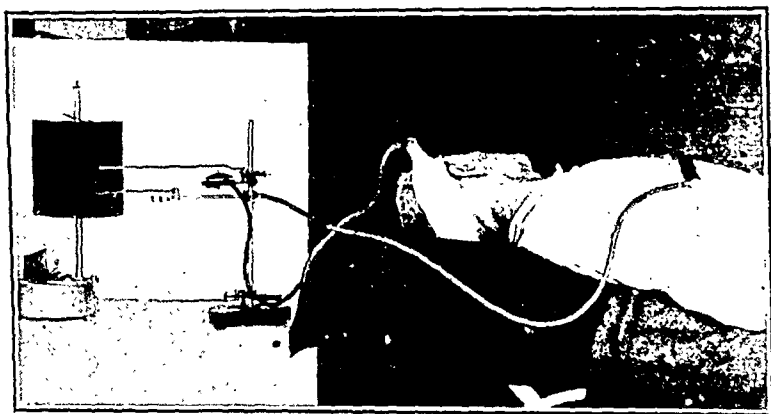
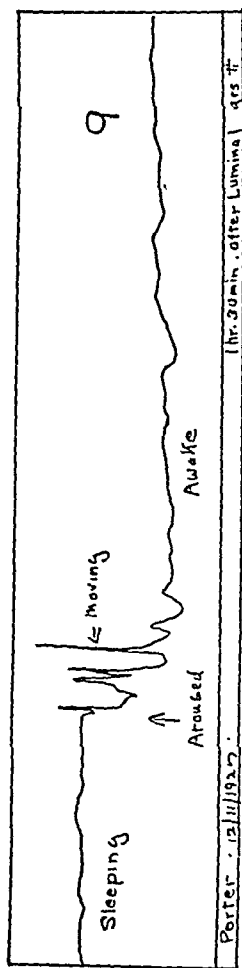
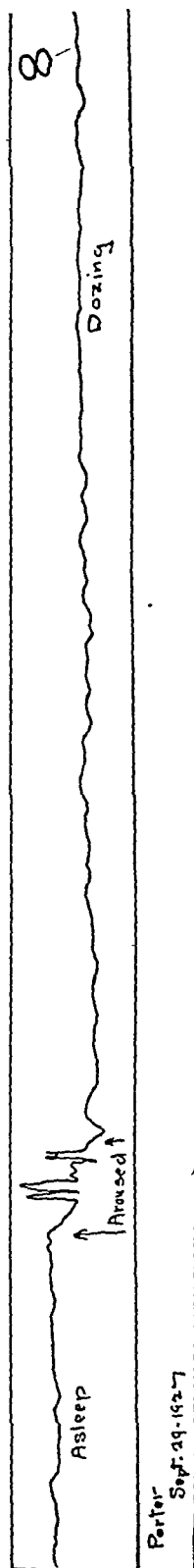
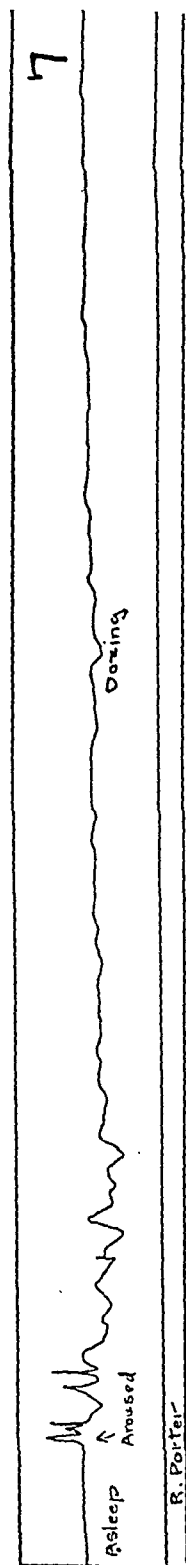


FIG. 1.—Apparatus applied over the brain hernia with the patient lying down.

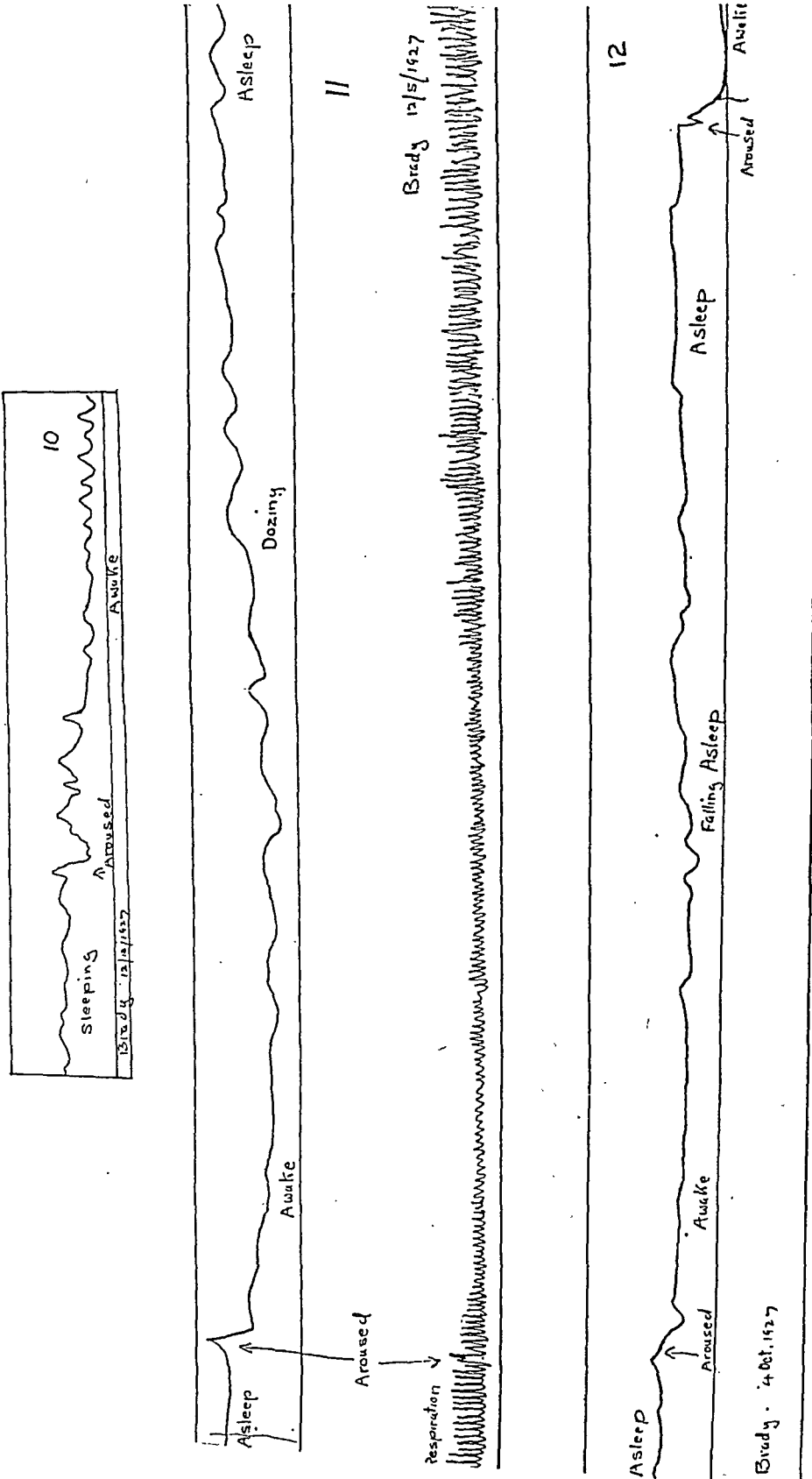
Figure 19 shows the effect of glonoin  $\frac{1}{160}$  gr. given sublingually. The effect lasted about twenty minutes with a corresponding fall in blood pressure.

Figure 21 was made on a case of Jacksonian epilepsy with almost continuous fits. Gas-oxygen-ether anesthesia was induced and maintained for one hour. The fits stopped in about two minutes and did not recur until the patient awoke, about five hours later. At the end of thirty minutes of anesthesia the intracranial pressure reached its maximum, this level being maintained for the rest of the hour and it was the same as the level at the peak of the fits. When the anesthetic was stopped, the pressure fell considerably but was still not quite normal at the end of forty-five minutes. The blood pressure fell from 136 systolic, 80 diastolic to 122 systolic, 80 diastolic during the anesthesia. Figure 22 shows that chloroform kept the intracranial pressure at a level equal to that during the peak of the fit. Chloroform was given about thirty minutes, and five



FIGS. 7, 8 AND 9.—The difference between the intracranial pressure during sleep and while awake. The first part of each curve shows the pressure during sound sleep—the uneven part of the curves is caused by the process of being awakened. When the patient is fully awake the pressure continues at a low level. In the last portion of Fig. 7 the pressure is seen to rise gradually as the patient falls asleep again.

NOTE.—On account of insufficient space it has been necessary to omit a number of figures that were originally included.



Figs. 10, 11 and 12.—Three more sleep curves. Fig. 11 shows the respirometer reading at the bottom. Fig. 12 also shows two periods of sleep.

minutes after it was stopped the patient began to have fits again, although the intracranial pressure had not fallen appreciably. Ether anesthesia was then started and the fits stopped, but the pressure in the head fell considerably. Ether was given for thirty minutes. After the ether was stopped the pressure again fell and the fits recurred one hour later.

Figure 23 shows the effect of morphin given subcutaneously in a dose of  $\frac{1}{4}$  grain. Five minutes after the injection the pressure began to rise gradually, reaching its maximum at the end of twenty minutes. The effect lasted about eighty minutes. There was no change in blood pressure. Since morphine increases the intracranial pressure, it would be safer not to administer it for the relief of headache in brain tumor.

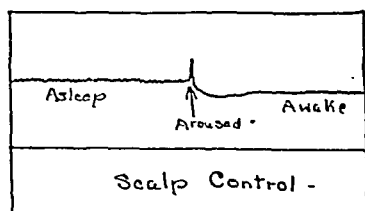


FIG. 15.—Scalp control taken during sleep.

Figure 30 shows the effect of  $2\frac{1}{2}$  grains of caffeine sodiobenzoate intravenously. The pressure began to fall at the end of one minute and reached its minimum at the end of three minutes. The effect gradually wore off, lasting about twenty-seven minutes altogether.

Figure 31 shows the effect of 5 gr. intravenously. There was an immediate fall with its greatest effect at the end of three minutes and lasting about twenty-five minutes altogether. In none of these experiments with caffeine was there any change in blood pressure.

Figure 42 shows the effect of 2 and 3 minims of adrenalin by vein. There was an immediate fall in pressure, together with a rise in blood pressure and an increase in amplitude and force of the hernial pulsation. These conditions lasted about three minutes and were followed by normal blood pressure and pulsation, but there was a delayed increase of intracranial pressure lasting more than twenty minutes. Figure 41 shows the effect of 4 minims by vein. There was an immediate rise in the intracranial and in the blood pressures, closely followed by an increase of amplitude and force in the hernial pulsation. These conditions lasted five minutes and were followed by a normal blood pressure and hernial pulse, and a delayed rise of intracranial pressure which was still at its maximum at the end of fifteen minutes. With 2 minims intravenously the blood pressure was increased from 100 systolic, 64 diastolic to 124 systolic, 70 diastolic; with 3 minims to 156 systolic, 74 diastolic; with 4 minims to 190 systolic, 110 diastolic.

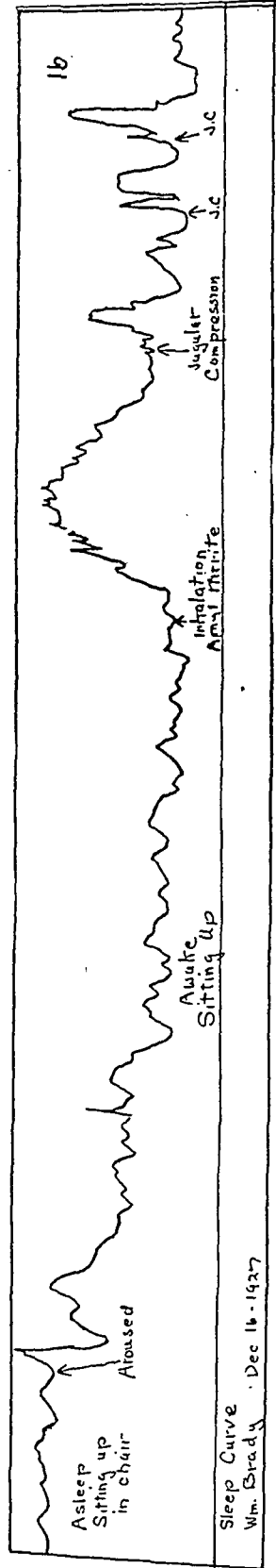


Fig. 16.—A sleep curve made while the patient was sitting up in a chair. This curve shows also the effect of amyl nitrite and jugular compression on the intracranial pressure.

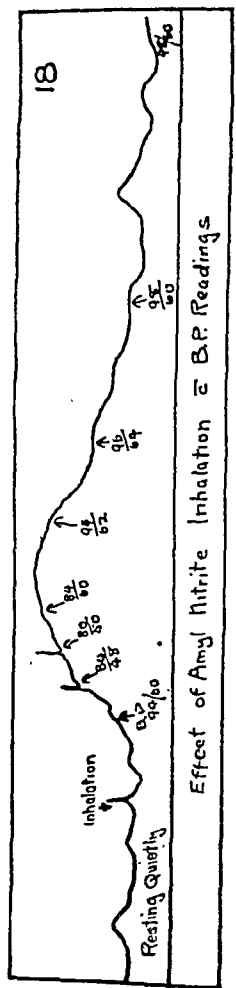


Fig. 18.—The effect of amyl nitrite with blood-pressure readings.

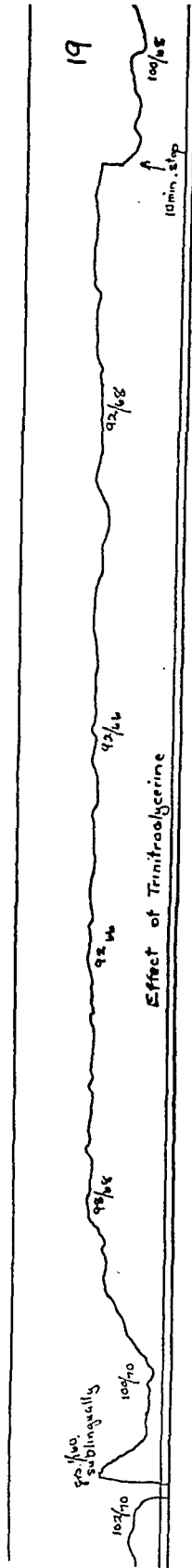
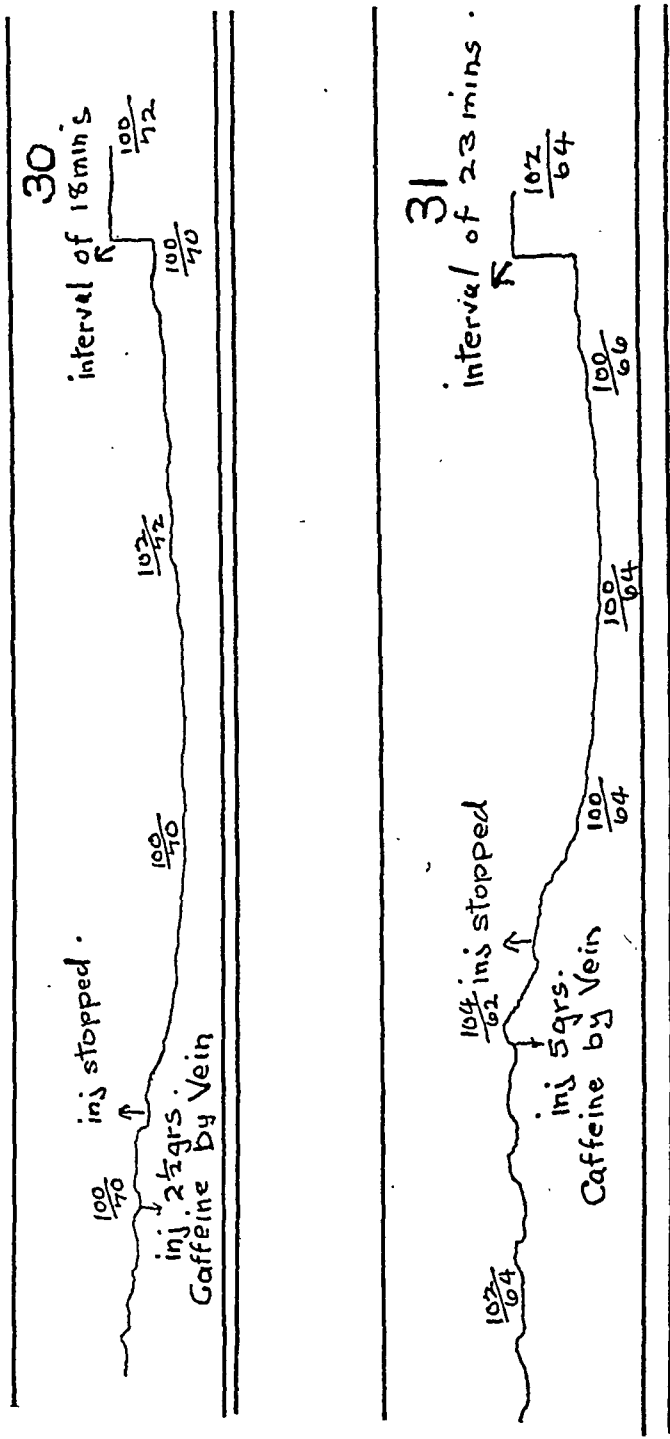


Fig. 19.—The effect of glonoin with the blood-pressure readings.



Figure 54 is a tracing of the changes in the intracranial pressure taken during a series of fits in a case of Jacksonian epilepsy. Twenty



Figs. 30 and 31.—The effect of caffeine-sodio-benzoate intravenously with blood-pressure readings.

minims of paraldehyde were given by vein during the fits with no apparent effect. Hypertonic glucose solution was given by vein on two occasions to this patient. The intracranial pressure showed a



slight fall, but in each instance the fits became more frequent and severe. This patient was later found to have a brain cyst near the hernia.

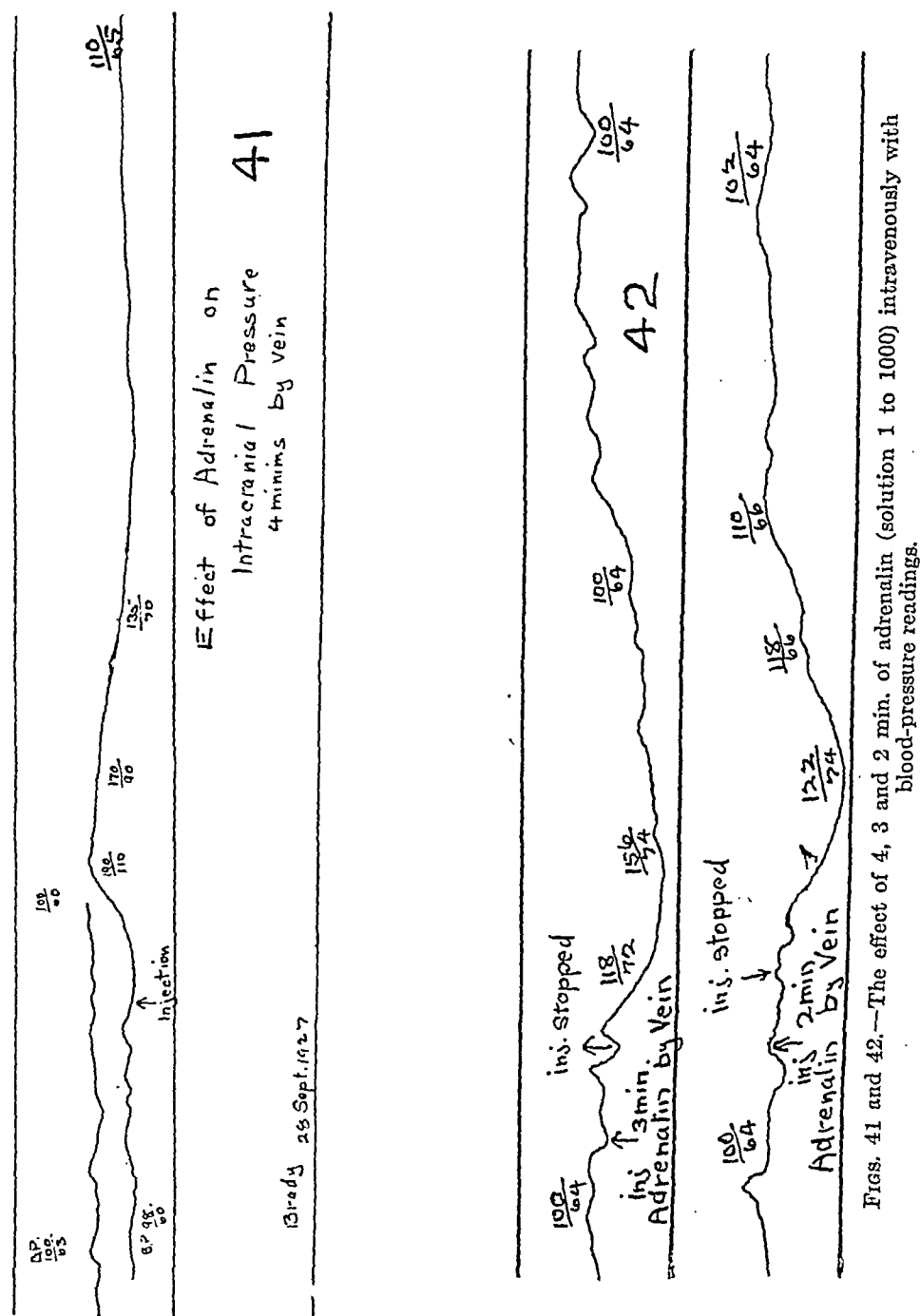


Figure 58 shows calibration. The apparatus was applied and a tracing made with the patient (Brady) at rest lying down. The

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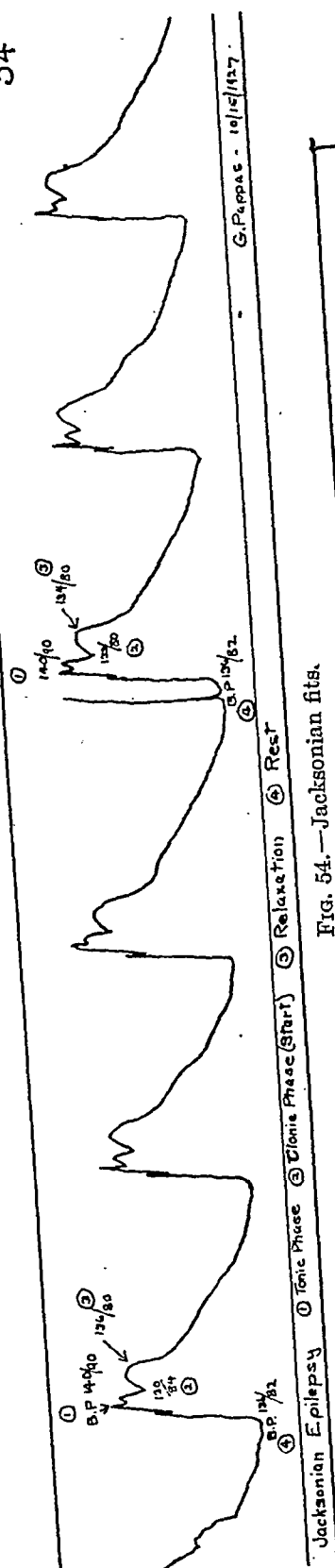


Fig. 54.—Jacksonian fits.

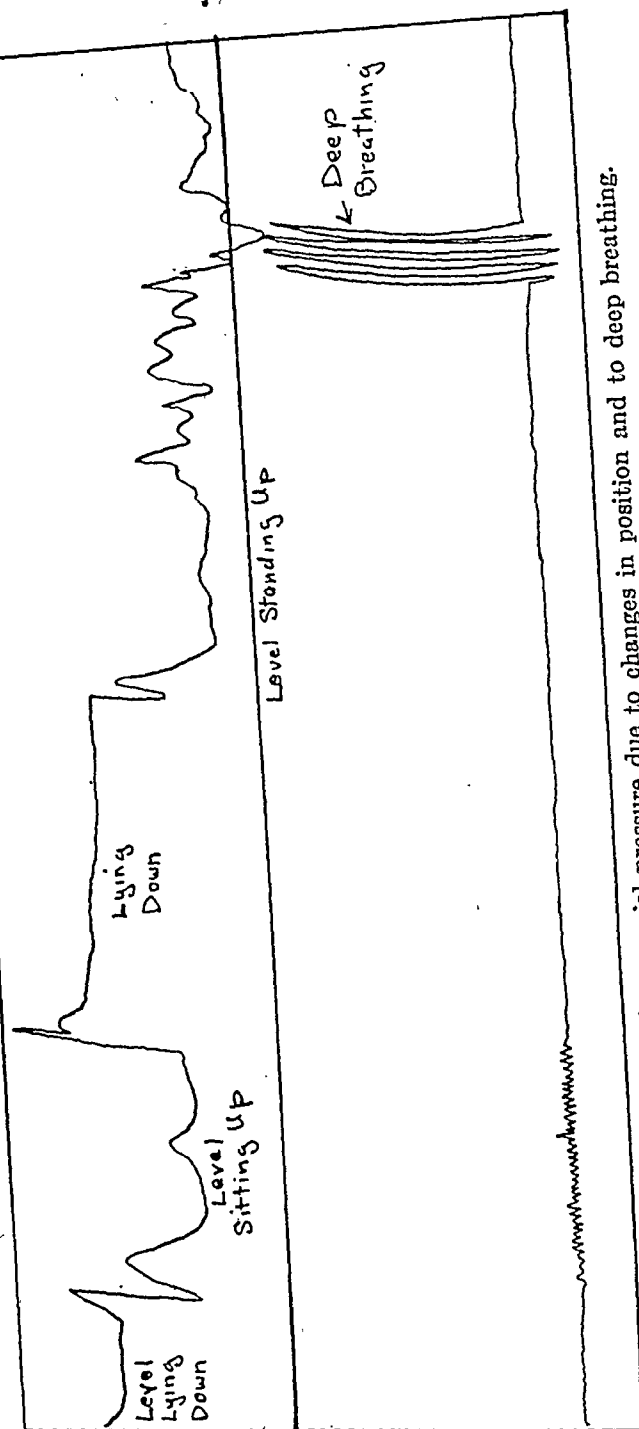


Fig. 56.—Changes of intracranial pressure due to changes in position and to deep breathing.

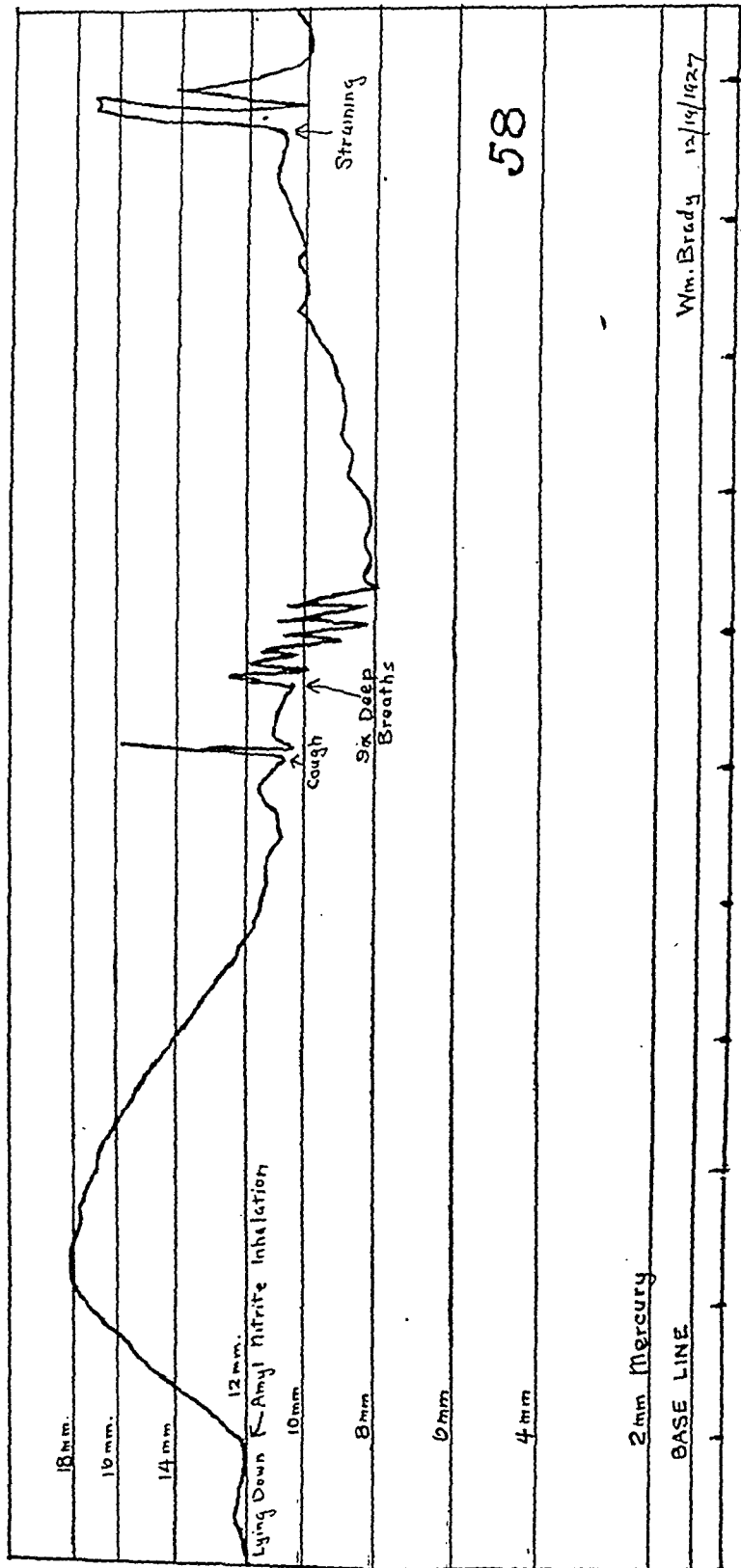


Fig. 58.—Calibration of the apparatus. The black dots at the base represent minutes and the horizontal lines represent each 2 mm. of mercury.

tube was then cut and connected with a mercury manometer (Baumanometer). The air pressure was again reestablished within the apparatus so that the pointer reached the original level; this pressure was found to be 12 mm. of mercury. Amyl nitrite was then given (5 minims by inhalation), causing a rise equivalent to 6 mm. of mercury. A cough caused a rise equal to 5 mm. of mercury. Deep breathing (6 deep breaths) caused a fall of 3 mm. of mercury. Straining caused a rise of 6 mm. and a secondary rise of 3 mm. of mercury. Each ruled division represents 2 mm. of mercury. The dots along the base represent one-minute intervals of time. A sleep curve, according to this calibration, would mean that the intracranial pressure is raised from about 2 to 6 mm. of mercury, depending on whether the patient is lying down or sitting up when he falls asleep. The difference of pressure in the head between the sitting-up position and lying down is about 4 mm. of mercury.

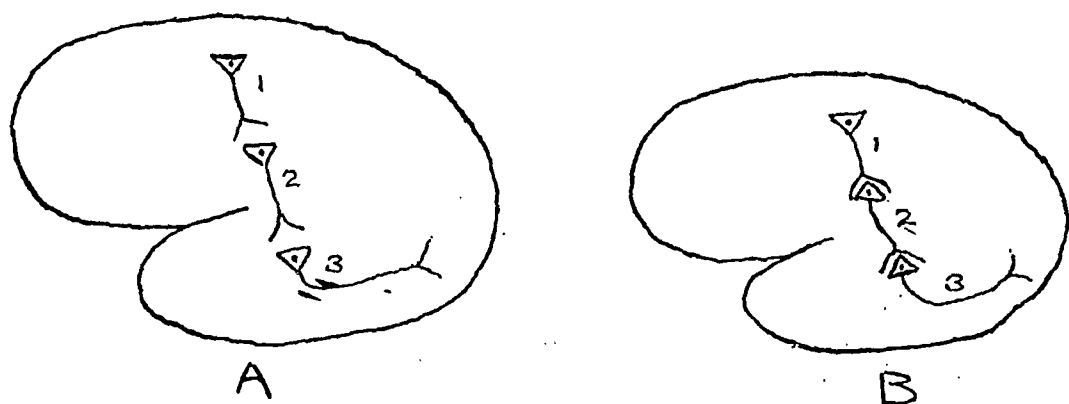


FIG. 59.—A, presumable condition of brain during sleep with conduction of impulses blocked because of separation of neurons 1, 2 and 3; B, brain in waking state or, under the influence of caffeine, with neurons more closely in contact and passage of impulses facilitated.

Figure 59 is a diagram to illustrate the mechanical effect of dilation of cerebral capillaries.

Some other tracings were made following the administration of luminal, bromid and chloral by mouth, but these showed no effect on the intracranial pressure within an hour.

Our experiments on the effect of drugs on the intracranial pressure have all been repeated one or more times and the effects demonstrated above have been constant. In addition to these drugs, pituitrin, adrenalin, ephedrin sulphate and hyoscin were given subcutaneously and showed a delayed but prolonged rise in intracranial pressure. Atropin and pilocarpin given subcutaneously caused little change. Hypertonic glucose solution by vein and magnesium sulphate by rectum caused slight fall in intracranial

pressure that was not nearly so great as that produced by caffein. Caffein given subcutaneously caused a definite fall of intracranial pressure that was still present at the end of forty minutes.

A few observations were made with the spinal manometer. The basic spinal fluid pressure with the patient lying down was 150 mm. of spinal fluid. Five minims of amyl nitrite caused a rise to 285 mm. Two minims of adrenalin by vein caused a slow rise to 205 mm.; the blood pressure rose from 105 systolic to 165 systolic. Deep jugular compression for ten seconds caused a rise to 350 mm. With the patient sitting up and his head erect, the pressure rose to 470 mm. Caffeine sodiobenzoate intravenously ( $2\frac{1}{2}$  grains) caused a fall to 120 mm.

In another patient 3 gr. of caffein sodiobenzoate by vein caused a fall from 155 to 119 mm.

Following these observations, caffein has been used during brain operations at Bellevue Hospital in order to reduce the intracranial tension before opening the dura. Caffein sodiobenzoate has been given intravenously in doses of 6 gr. for this purpose. This principle may also explain why caffein relieves headache due to brain tumors.

**Conclusions.** 1. The intracranial pressure is increased during sleep. The pressure gradually rises until the patient is sound asleep, when the curve reaches its maximum, and this is maintained at a fairly constant level during sound sleep. On awakening the pressure falls rather rapidly again to normal.

2. There is an increase of the intracranial pressure on lying down (Fig. 56).

3. Partial sleep or drowsy states are associated with a rhythmic increase of the intracranial pressure which is not so high as during sound sleep.

4. Certain drugs which are known to affect the nervous system as sedatives or as stimulants depend in part for their effect upon a hitherto unappreciated mechanical factor, namely, an increase or a decrease of the intracranial pressure. For example, morphin, a sedative, causes an increase of the intracranial pressure, while caffein, a stimulant, produces a fall.

5. The intracranial pressure is, within wide limits, independent of the blood pressure.

6. Our conception of the physiology of sleep, arrived at from a study of our experiments and those of other workers, is as follows:

We believe that the sympathetic center in the brain which maintains vasomotor tone in the vessels becomes periodically fatigued. This results in a vasodilatation of the bloodvessels of the brain, as well as those of the periphery. Accompanying this, as further evidence of fatigue in the sympathetic system during sleep, are the constricted pupil, the slower heart rate, and the decrease of blood pressure. This vasodilatation in the brain would result in one of two things:

(a) The brain volume would be increased with a consequent pulling apart of the neurons (diaschisis). This might result in a physiologic interruption of function in the manner suggested by Cajal and Duval when they assumed that the dendrites of the nerve cell were contractile.

(b) The pressure of the cerebrospinal fluid within the brain would be increased and especially in the pericellular spaces, thus altering the conductivity of the synapse.

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## CONVULSIVE STATES.

### A CLINICAL STUDY OF UNUSUAL PHENOMENA, ETIOLOGY, DIFFERENTIAL DIAGNOSIS, AND TREATMENT.

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IN routine office examinations of the past three years G. A. Young and I have examined over 200 patients in convulsive states. A study of these records reveals numerous facts of interest to any practitioner called to attend a convulsive case.

The examination of a convulsive state demands, because of the grave and severe symptom involved, not only a careful physical and neurologic examination but also complete laboratory studies. The extent of these studies should be determined by a careful analysis of the case history and should include, wherever indicated, Roentgen rays, blood chemistry, metabolic tests, allergy studies, feces analysis, spinal-fluid pressure, cell count, protein estimation, Wassermann test, and Lange gold curve. At times encephalography is necessary. The large majority of the cases here reviewed were hospitalized several days for complete examinations. Sometimes direct observation of the seizures was indicated in order to determine the character of convulsions and to reach an accurate diagnosis.

Of our 200 cases, 124 were classified as essential epilepsy including status epilepticus. Of the remaining 76, 11 cases were hysterical; 9 were listed under traumatic causes; and 56 cases of epileptiform seizures were considered of organic pathogenesis. In this last class were: Brain tumor, 10; brain abscess, 2; cerebrospinal syphilis, 7; encephalitic or meningitic sequelæ, 5; infantile cerebral palsy from birth hemorrhage, 8; cardiovascular disease, 9; organic and toxic of obscure etiology, 11; narcolepsy, 4.

**Etiology of Essential Epilepsy.** Of various hypotheses with regard to the etiology of essential epilepsy, it seems certain that no single

etiologic factor will ever explain all cases. The hereditary influence, present in 40 per cent of our epileptic group, is a definite factor in many instances. Psychogenesis is offered by some as an explanation. Various chemical toxins, for example, strychnine, oxalic acid, or absinthe poisoning, and unknown or obscure toxemias, such as pregnancy, uremia, allergic sensitization, and so forth, are capable of producing convulsions. Endocrine glands, such as pituitary disorders, have been suspected, certain metabolic changes, such as hypoglycemia, disturbed calcium metabolism (spasmodophilia), linked also with the endocrine dysfunctions, produce convulsions. Robinson, Brain and Kay<sup>1</sup> have recently found the blood cholesterol to be low in epileptics and to fall just prior to the onset of a convulsion, the fit taking place at the lowest point. No explanation of this abnormal metabolic phenomenon was given. Functional circulatory disturbances, blood-pressure changes as seen in fainting, heart block, and so forth, produce epileptiform spasm.

Hughes,<sup>2</sup> studying the effect of deficiency on vitamin A in mother's diet upon the brain of a fetus, reports a disorder of the nervous system, produced in young pigs by a diet free from vitamin A., consisting chiefly of ataxia, blindness, paralysis and convulsions. Dandy<sup>3</sup> has demonstrated on dogs that injury to the motor cortex lowers the threshold for the production of convulsions. Dogs so injured convulsed after one-third to one-seventh of the dose of absinthe necessary to produce convulsions in normal controls.

Ziegler<sup>4</sup> suggests from this work that idiopathic epilepsy is probably the result of injury to the brain which enables smaller insulting agents to induce convulsions. Injury probably occurs early in life and must be insidious and obscure to escape detection. In the light of recent work on vitamin deficiency the health of expectant mothers and the food of children should be given every consideration to prevent the type of injury to the brain that never can be repaired.

The multiplicity of factors producing convulsions illustrates the complexity of the problem of the pathogenesis of essential epilepsy and the reason for its obscureness. There are many factors as yet undiscovered.

**Factors Promoting Epileptic Seizures.** While it is generally believed by authorities that the essential epileptic is constitutionally predisposed to convulsive seizures (that is, the epileptic constitution), there are many factors that apparently precipitate seizures or aggravate seizures already present. A common observation in children is (in certain types) the occurrence of convulsions with each febrile upset. The finding of these factors such as Gordon's<sup>5</sup> careful study gives a lead in the treatment of the epileptic. In our group 26 cases (20 per cent) presented definite physical factors, such as definite focal infection or a history of convulsions following systemic infections or toxemias. Five cases fell into definite endocrine groups.

**Relation of Infantile Spasms to Adult Epilepsy.** In the considerable literature upon the subject, one finds but few careful statistical reports in comparison with normal controls. Opinions differ widely, according to the point of view. Many pediatricians, finding no relationship between ordinary infantile spasm and later more serious mental disturbance or convulsions, seemingly underestimate the significance of childhood spasms. Possibly the neurologist tends to overemphasize the significance.

Patrick and Levy<sup>6</sup> in a comparative study of 500 epileptics and a normal group of 751 infants concluded that convulsions (not epileptic) in infancy and childhood are evidence of the individual's tendency to later epilepsy. They found 20 per cent of their epileptic group had early convulsions and about 4 per cent in the control group. They believe their percentage was too low because of failure of patients or relatives to recall early spasms after the patient reached adult life. In general, they found the younger the epileptic the higher the incidence of infantile spasms in the history. The more likely forerunners of epilepsy are convulsions: (1) occurring before six or after eighteen months; (2) multiple; (3) severe (4) localized; (5) assigned to birth trauma, reflex causes or no cause; (6) with a family history of epilepsy or similar convulsions. The most significant are unilateral convulsions occurring after the fourth year, and generalized convulsions lasting over half an hour and followed by confusion or torpor for several hours. Especially benign appear to be "teething spasms" occurring between eleven and thirteen months.

Thom<sup>7</sup> found a much higher incidence of infantile convulsions in a study of 300 cases from an epileptic hospital; of these 50 per cent had convulsions prior to the fourth year. From study of another group with convulsions not diagnosed as epileptic, considered to be caused by acute infections, and so forth, before the fourth year, Thom concludes that the type of nervous system that reacts with convulsions in the presence of mild toxemia associated with gastrointestinal upsets is perhaps the type of nervous system that needs protection from environmental situations. Thus convulsions may perhaps be considered as the criterion of the stability or instability of the nervous system. His conclusions were based upon the fact that 56 per cent of these supposed nonepileptic infantile convulsions were malignant; either continued to death, typical epilepsy developed or the children were mentally deficient.

In our group 16 out of 124 (15 per cent) gave a history of infantile spasms. This percentage is undoubtedly too low. About half our cases were examined after twenty-one years of age. In many instances, accurate childhood history was not obtainable and parents were not present. Infantile convulsions should be considered seriously and parents so informed, since it seems likely that about 50 per cent will become epileptic or its equivalent.



**The Relationship of Trauma to Epilepsy.** The relationship of head trauma to the development of later epilepsy is exceedingly puzzling. In certain cases, evidence of a definite localized lesion can be found shortly after the trauma in the nature of hematoma from skull fracture or meningeal apoplexy. Here the convulsions usually are of Jacksonian type and early surgical intervention indicated. In a much larger group of cases the head trauma may be mild, yet serious convulsions follow that show no organic signs or pressure phenomena. In this group the accepted explanation by most authorities is that a previous epileptic predisposition has been excited into a frank epilepsy by the trauma. The more recent work of Dandy<sup>3</sup> showing lowered cortical threshold to convulsions after trauma of the motor cortex throws more light on the cause of these cases.

In our series there were 9 (4.5 per cent) that had convulsive seizures following head trauma. Four had localized findings of organic brain injury or hematoma formation. Two of these had had one or more decompression operations without relief of the spasms, since the residual brain lesion in the form of cicatrices is not benefited by surgery. Increased pressure is the safest criterion for decompression. In 2 cases the convulsions ceased after the acute pressure phase of the concussion subsided. The remaining 3 cases showed no organic signs; 2 of these had Jacksonian convulsions.

**Petit Mal Attacks.** A diagnosis of petit mal epilepsy is frequently missed, probably because of uncertainty of what constitutes a petit mal attack.

It is important to study carefully slight nervous tendencies in children. Sudden momentary stares, sudden feelings of fright, sudden tastes or smells, a causeless stop in play, laughing spells, sudden bobbing of the head or dropping to the floor, sudden sensations of unsteadiness or falling or transient dreamy spells may all be manifestations of epilepsy.

An example of an atypical petit mal type is as follows:

**CASE I.**—Male, aged forty-four years, with a familial history of epilepsy, for fifteen years had been troubled with peculiar vertiginous-like attacks (a sudden sensation of falling or unsteadiness many times a day), causing him to avoid social contacts and embarrassing him greatly at work. Organically there was a rheumatic endocarditis present. Phenobarbital controlled the attacks almost completely. After two years' observation the patient died of cardiac decompensation. Necropsy showed a marked aortic stenosis.

**Status Epilepticus.** The development of convulsions in series is always a serious condition and in many of these serial types the convulsions come closer together with unconsciousness between the attacks, so-called status epilepticus. In our group, there were 4 cases (3 per cent) that developed status epilepticus. Two died, one in the first attack of status and one in the second. Two were

adults with onset after thirty-five years, one, a girl, aged seventeen years, had 140 Jacksonian convulsions in twenty-four hours. Exploration revealed no definite lesion of the motor cortex. The surgeon thought he could palpate a deep softened area.

**Mental Disturbances in Epilepsy.** A large percentage of essential epileptics develop some mental disturbance. These mental reactions vary from dullness, difficulty in thinking and memory impairment, behavior oddities, acute psychotic outbursts of extreme violence, to profound mental and emotional deterioration. Transitory psychotic states are common preceding, following, or replacing the seizures, so-called psychic equivalents. At times manic excitement or wild states of blind rage or furor during which the epileptic may attack any one. Upon regaining his normal mental status, the epileptic has no recollection of the acts.

We found 22 (18 per cent) of the 124 essential epileptics showed distinct mental reactions aside from the usual epileptic personality.

The following case illustrates one type of psychic equivalent:

**CASE II.**—Male, aged eight years, developed serial grand mal attacks at weekly intervals from three until seven years. Petit mal daily seizures then commenced. Each attack was followed by "angry, mean" spells that lasted several hours. Overactivity and motor restlessness progressed to the point of incontrollability. School progress was *nil*. The personality change was profound. The Binet-Simon test showed an I. Q. of 100, no organic factors were found. The general condition of the patient was worse while taking phenobarbital. Coincident with changing the intestinal flora by acidophilus preparations and a combination of bromids and belladonna his attacks ceased and normal behavior and school progress followed. For four years the patient has remained normal and free from seizures.

**Migraine and Epilepsy.** The relationship of migraine and epilepsy seems to be that of "first cousins." It has long been observed that migrainous heritage often produces epilepsy. The occurrence of both conditions in the same patient is not unusual. Phillips<sup>8</sup> classifies the cases in three types: (1) migraine occurring during early life, ceasing at menopause, and epilepsy developing later; (2) the group with epilepsy in earlier years and migraine later; (3) migraine and epileptic attacks alternating. He believes both conditions are due to cardiovascular disturbance and the relationship is coincidental. Flatau<sup>9</sup> found both conditions in 36 patients in a group of 500 epileptics.

In our group, definite migraine history in the family occurred in 12 (10 per cent). A double strain of migraine occurred once. While some of the records did not inquire specifically for both conditions in the same patient it was noted in instances; in each of these they were closely associated, usually alternating.

**Jacksonian Convulsions.** Focal or Jacksonian spasms occurred in 16 cases (13 per cent) of this series. Twelve cases of Jacksonian seizures were definitely from organic brain disease, usually focal

disease of the cortex, 3 cases followed birth hemorrhage, 3 followed vascular accidents (hemiplegias), 2 followed severe head trauma, 1 focal meningitis or encephalitis, and 3 cases from brain tumor. In four instances the Jacksonian spasms were essentially epileptic without demonstrable cause.

Wilson,<sup>10</sup> Collier, Mills and others have emphasized that Jacksonian convulsions are common in essential epilepsy. They go so far as to state that idiopathic epilepsy is the commonest variety of Jacksonian attacks. Wilson gives the warning, with which I agree, that Jacksonian cases should not be operated upon without definite evidence of intracranial disease. It is a much safer attitude, on the other hand, to consider all Jacksonian seizures as organic in nature until definitely proved otherwise and only by exclusion of all factors to call them essential epilepsy. A fair percentage of idiopathic epilepsies in the earliest seizures start as Jacksonian attacks and later become typical generalized convulsions. It is probable that each convulsion at its very onset is Jacksonian but quickly spreads bilaterally.

**Hysterical Convulsions.** Convulsive states are often one of the prominent motor symptoms of conversion hysteria. At times the differentiation from essential epilepsy is baffling. Certain cases seem to be a cross between the two conditions, thus leading to the hyphenated expression of hysteroid epilepsy. When this occurs I personally believe we have two conditions—an hysterical personality having true epilepsy. It is well known that organic diseases frequently have a psychoneurotic coloring.

The characteristic march of symptoms of sudden onset, always followed by unconsciousness in epilepsy, with usually some trauma to lips, tongue or body during the convulsions and with at times incontinence, usually labels the picture epileptic, not hysterical. In the hysteric, the convulsion is always psychogenetically determined, an exciting emotional cause usually present, without complete loss of consciousness but rather a fugue state of dissociation with amnesia following.

There were 11 cases (5 per cent) in our series of convulsive states of hysterical origin. In one unusual case during the tonic spasm hyperpnea developed to a degree that artificial tetany was produced from overalkalinization of the blood.

**Narcolepsy.** Strictly speaking, narcolepsy is not a convulsive state but its manifestations are epileptiform and by some it has been considered a form of epilepsy. These patients suffer from spells of dropping off to sleep which they are unable to control, and they frequently fall asleep under most inopportune conditions. In addition they suffer from sudden weakness of body musculature simulating paralysis during emotional disturbances such as laughter, anger, or excitement. Under emotional stress they suddenly lose all motor power and the legs give way, the patient usually falling

to the ground. This condition is called "lachtschlag" by the Germans. Henneberg described it as cataleptic paralysis.

Spiller<sup>11</sup> and others have described this syndrome following encephalitis. In one of our patients the syndrome followed encephalitis. While narcolepsy is a relatively rare condition more cases than usual have been seen the last few years by all observers.

The following are illustrative cases of this condition:

CASE III.—Mr. J. M., aged forty-four years, a short time before our examination noticed attacks of sudden loss of motor power with some cramping of the muscles when endeavoring to carry out sudden movements while under emotional tension. This symptom had been noted particularly while hunting ducks, when ready to pull the trigger his body suddenly weakened, paresis of the arms developed, and he dropped the gun. Laughter or anger caused the entire body to weaken and at times to fall, the power of speech was lost during the spells. Narcolepsy had not developed.

A complete examination revealed no evidence of neurologic disease. This patient has noted a very definite improvement in the symptoms while taking continuous small doses of phenobarbital. When he ceased taking the drug the symptoms promptly returned.

CASE IV.—Mr. R. R. R., aged thirty-one years, received on top of the head of a severe blow from a 40-pound weight. No unconsciousness followed and work was resumed the following day. Within two weeks after the accident typical spells of falling to sleep began. At the same time spells of muscular collapse from emotional stimulation began, for example, while correcting the children, attempting to chase a dog, while laughing, or from fatigue he would fall to the ground. In addition, he had noted momentary semiconscious spells associated with twitching of the facial muscles, motor weakness and loss of power of speech. Excitement of attempted coitus produced semiconsciousness and muscular quivering with loss of power which prevented him from completing the sexual act. At times the patient had involuntary urination during the spells. The family physician described what seemed to be a generalized convulsion following one attack.

Prolonged observation has failed to reveal any evidence of organic disease. Deep Roentgen ray therapy over the hypothalamic region was tried without improvement.

**Convulsions of Cardiovascular Origin.** Riesman and Fitz Hugh<sup>12</sup> consider that *epilepsia tarda* includes a group of convulsive states having their onset after forty years of age. Cases without etiologic factors other than a periodic insufficiency of the cerebral circulation, they divided in three groups: (1) arteriosclerotic; (2) hypertensive; (3) mixed hypertensive and arteriosclerotic. They report 12 cases having the average age of onset thirty-six years. Because of underlying circulatory abnormality in all cases, they concluded that momentarily deranged cerebral circulation (cerebral anemia) was the exciting cause. Many died apoplectic deaths. They found convulsions in uremia to be rare and usually a terminal state.

In the cardiovascular group of our series I have listed 9 cases (7.2 per cent), 5 of which had onsets after forty-five years and

showed definite arteriosclerosis, with or without hypertension and myocardial degeneration or valvular defects. Two patients had associated mitral stenosis. One had an embolic apoplexy with residual Jacksonian convulsions, one syncopal attacks with cardiac insufficiency signs; both of these had their onset in the thirties. One case of meningeal apoplexy was followed by convulsions; one cortical vascular softening with right hemiplegia after head trauma was disclosed at operation.

**Convulsions from Cerebrospinal Syphilis.** Syphilis as a cause of convulsions has probably been overemphasized. Older textbooks classify convulsions beginning in middle life as usually from neurosyphilis. We do not find this to be true.

Cerebrospinal syphilis was found in 7 cases (3.5 per cent) of the entire group. Occasionally convulsions in children, the result of juvenile paresis, are overlooked and considered essential epilepsy. Two cases in this series were juvenile paretics. Two were adult paretics. Convulsions often give the first warning of approaching paresis. Three cases were meningovascular cerebral syphilis. Any convulsive disorder beginning in adult life should be closely observed for organic brain disease, and syphilis excluded by spinal-fluid studies.

**Convulsions in Infantile Cerebral Palsy from Birth Hemorrhage.** Mental retardation, hemiplegia and convulsions, one or all usually follow cerebral hemorrhage at birth. Children suffering from this unfortunate accident rarely survive without some sequelæ.

There were 8 (4 per cent) of this series of convulsive states that definitely were caused by birth hemorrhage. Five cases had a history of instrumental delivery, 2 prolonged difficult labors, 1 premature delivery. In 5 cases with hemiplegic findings the convulsions were unilateral Jacksonian type.

**Convulsions in Brain Tumor and Abscess.** These convulsions may be either an early irritative symptom, sometimes being present for years before other signs of tumor occur, or a late pressure manifestation. Convulsions in brain tumor are at times of localizing value, since they are common in tumor of the anterior chamber and unusual in posterior fossa tumor; more frequent in temporal lobe neoplasms than in occipital; easily caused by tumors growing near the motor area. Convulsions resulting from increased intracranial tension are of little localizing value.

There were 12 instances (6 per cent) in our series of convulsions from proved brain tumor or abscess. Two were brain abscesses, both in the temporal lobe. Of the tumors 6 were in the frontal or frontotemporal areas, 1 pituitary, 1 temporal lobe, 2 unlocalized. In 4 cases the convulsions (focal spasms of diagnostic value), were among the first symptoms, in 1 case preceding by nine years other definite symptoms of tumor. In 5 cases the convulsions were generalized, all showed high manometric pressure readings upon lumbar puncture and later proved to be tumor.

Examples of this type are as follows:

CASE V.—Male, aged thirty-five years, began having very severe attacks of generalized convulsions in series with no objective signs. Mental deterioration progressed after each series. Spinal puncture showed a pressure of 40 mm. of mercury after a convulsion, the fluid was slightly bloody. Decompression was done but death followed. Necropsy revealed a large soft glioma of the right frontal lobe.

CASE VI.—Male, aged forty-five years, had generalized convulsions for several years without localizing signs. The spinal-fluid pressure was 20 mm. of mercury. Aphasia and right hemiparesis developed. Operation disclosed a cystic glioma in the left motor zone. Marked functional improvement for two years followed by intermittent pressure signs developed, each time accompanied by convulsions.

**Convulsions from Cerebral Inflammations.** The occurrence of convulsions in acute meningitis is a common symptom, particularly in children, and in the more fulminating types is usually a grave sign. Residual convulsive states are frequent following a purulent meningitis in which external hydrocephalus or localized adhesive exudates remain, producing irritative lesions, lowering the nervous threshold of nervous irritability, and predisposing the individual to later epilepsy. In our series were 5 cases (2.5 per cent) of convulsions definitely traceable to encephalitic or meningitic processes.

**Convulsions Occurring in Obscure Toxic or Organic Cases.** In this group an accurate organic diagnosis was not possible in 11 cases (5.5 per cent). Four of these were probably vascular in origin of which one had a history of syphilis but negative serologic findings, and in all of which the onset was after forty years. Two cases suggested strongly brain tumor but were not proved. Two cases were from obscure cerebrospinal infections, one probably serous arachnoiditis, had a temporary cerebrospinal block with increased spinal pressure. The condition gradually subsided. The other resembled epidemic encephalitis. One child, aged four years, had a premature closure of the fontanelles with increased spinal pressure. Another patient had evidence of toxic convulsions from an obscure systemic infection. One patient had severe serial convulsions associated with hyperglycemia and mild nitrogen retention but without marked acidosis, apparently a toxic reaction the forerunner of diabetic coma.

**The Management of Convulsive States.** The first step in intelligent treatment of a convulsive state is obviously the finding of any etiologic factors and removing these. Only by exclusion of all organic and toxic causes are we justified in calling the seizures essential epilepsy. The necessity of an accurate diagnosis is the paramount issue. Convulsions beginning in middle life challenge us to very detailed examinations and should be considered organic until we can find no demonstrable cause. Those that are found to

be organic (symptomatic epilepsy) indicate special therapy. Intracranial pressure conditions require neurosurgical therapy. Those cases resulting from neurosyphilis, arteriosclerosis, cardiac insufficiency, and so forth, require treatment directed toward the underlying cause.

There is a large group of organic cases that cannot be handled in any other way than by symptomatic sedative treatment. These should be managed the same as essential epilepsy. Many of these residual convulsive-form lesions of the cortex respond well to drug therapy.

It is through prevention only, including better prenatal care to prevent toxemia of pregnancy and better obstetrics during parturition, that the incidence of birth hemorrhage convulsive states can be reduced. Spinal drainage until the fluid is clear should be done in these cases to prevent residual cortical defects. Acute cerebrospinal inflammations, where remediable, offer a field in preventive epilepsy. Meningococci meningitis too frequently has epileptiform sequelæ. Earlier and larger doses of serum given intracisternally quickly sterilize the subarachnoid system before adhesive exudates produce subarachnoidal blockage, and residual convulsions. In the infantile spasm group, greater care of these potential epileptics as to nutrition, rickets, and so forth, and prevention of physical and mental excesses during the growing period, offer hope in preventing adult epilepsy.

*Hysteria.* In the hysterical convulsive patient drugs should not be resorted to, but psychotherapeutic treatment in the form of reëducation through psychoanalysis, hypnotic suggestion, or other psychotherapeutic measures are indicated. An attack should be made upon the underlying hysterical constitution that is overreacting to some emotional conflict, showing itself as convulsions.

*Post-trauma.* The post-traumatic convulsive case is sometimes a difficult therapeutic problem, particularly in cases of Jacksonian spasm. In general, I believe that operative interference is of no avail unless evidence of intracranial pressure is present. We see a fair number of patients of this type having had one or more decompressions without relief. Symptomatic sedative treatment the same as for essential epilepsy is indicated. Operative interference soon after the onset of convulsions might be more favorable but in the delayed case surgery offers but little hope.

*Narcolepsy.* In this interesting syndrome because of inaccurate knowledge we are in etiologic darkness. Spiller in a personal communication stated he had found nothing to relieve the condition. In one of our cases the patient found definite relief while taking phenobarbital.

**Symptomatic Treatment in Essential Epilepsy.** Drug therapy resolves itself largely into sedative treatment to lower the threshold of cortical irritability. Practically every hypnotic has had a trial

in epilepsy. The drugs in present favor are the salts of bromin, and phenobarbital which is probably the drug of choice with the majority of authorities. Chloretone has a place in certain resistive cases and belladonna has a definite place, particularly when combined with bromids for petit mal types.

*Bromids.* Each patient must be individualized. As Clark stated, our principle should be to treat the epileptic, not his seizures. In certain cases, bromids very effectually control the seizures, in other cases, the addition of belladonna or the administration of bromids and phenobarbital is necessary. The usual rule has been to give sufficient bromid up to about 60 gr. a day to control the seizures. We use a colorimetric method to determine the bromid content of blood serum as recommended by Wuth.<sup>13</sup> The dosage can be regulated to prevent bromid intoxication.

Clark<sup>14</sup> states that in certain cases it is contraindicated to give a large enough dosage of sedative to control the attacks. A relative cure is frequently advisable because a chronic inhibition of attacks often causes a cumulative outcome and changes the character of the case from a benign to a malignant type. In any case the earlier vigorous treatment before the chronic state is established offers the best permanent outlook. Every patient must continue sedatives for years after the seizures cease before reducing the dosage.

*Diet.* Practically every form of diet has been advocated in epilepsy. The most recent diet therapy is the ketogenic, increasing the fat content and reducing carbohydrates until acidosis ensues. Maintaining acidosis is supposed to inhibit the convulsions; it also regulates normal bowel action. Careful trial of this method in children has not yielded the permanent results hoped for and drug therapy has been a necessary adjunct. I do not wish to imply that we see no merit in this treatment, but we believe the earlier reports are overenthusiastic. I can see no reason for extreme restrictions in diet. It is advisable to restrict indigestible articles, spices and stimulants. Excessive sweets and meats with children are to be avoided. Certain cases have seemed to be benefited by changing the intestinal flora by the use of acidophilus cultures and lactose.

*Phenobarbital.* This drug controls many grand mal cases completely. It is less effectual in the petit mal type. Dosage up to 3 gr. a day is permissible, above this usually producing intoxicating symptoms. Many cases require only 1½ gr. each night.

*Petit mal Types.* Phenobarbital is often disappointing in this type. Many cases will respond when it is given with bromids. As stated before a combination of bromids with belladonna will relieve resistive cases. Where these measures fail, chloretone 2 gr. twice daily given with the other measures is helpful.

*Status Epilepticus.* Heroic measures are indicated in continuous serial convulsive seizures or a fatal result is likely to follow. Stren-



uous elimination is indicated, colonic flushing should be given at once. At times spinal drainage is helpful. Large doses of sedative are necessary. Sodium phenobarbital intravenously is the most effective in doses up to 10 gr. for adults. Ether and chloroform anesthesia are of but temporary value and often dangerous. Cardiac support, increased fluid intake to overcome dehydration, and other symptomatic treatment may be indicated. Inhalation of amyl nitrite should be tried.

*Migraine and Epilepsy.* Phenobarbital frequently relieves the migrainous state as well as the convulsions. The double problem is often resistive to therapy. We must treat the individual constitutional problem as presented, correcting any fundamental defects found. One patient was symptomatically cured after removal of focal infection and the administration of endocrine therapy for definite hypopituitarism and thyroidism. The administration of cannabis indica along with phenobarbital aids many migraine cases. Allergic investigation may reveal protein sensitization, thus giving a clue to dietetic treatment.

**Summary.** In a clinical study of 200 convulsive states, 124 were essential epilepsies, and 76 other convulsive states with known etiology. Of the epileptics, a neuropathic heredity was present in 40 per cent; in 20 per cent physical factors were noted that facilitated the seizures. In 15 per cent there was a history of infantile spasms. In 18 per cent were definite abnormal mental reactions. Migraine occurred in 10 per cent in the family history.

Of the 200 cases 4.5 per cent followed head trauma. Jacksonian spasms occurred in 8 per cent; 12 of these cases were organic spasms and 4 were essential epilepsies. Decompressive operations have not improved the organic unilateral spasms in this series. The safest indications for neurosurgery are pressure signs.

Five per cent of the entire series had hysterical convulsions. Four cases of narcolepsy with "lachs Schlag" or cataplexy were found in the series. Five per cent of the cases had convulsions beginning in the arteriosclerotic age with signs of cardiac insufficiency sufficient to be considered etiologic. Cerebrospinal syphilis was responsible for 3.5 per cent of the cases. Birth hemorrhage with associated cerebral palsy was present in 4 per cent, tumor and brain abscess in 6 per cent. Attention is called to the convulsions that are an early symptom of brain tumor, at times present long before pressure signs and of diagnostic value. Residual convulsions from cerebral inflammatory conditions occurred in 2.5 per cent of cases. There were 5 per cent of cases classified as toxic and mixed organic types with obscure etiology.

Various methods of treatment are discussed with emphasis upon the proper management of essential epilepsy and with attention to the possible ways of preventing convulsive states.

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## SPONTANEOUS INTRACRANIAL HEMORRHAGE FROM A VASCULAR TUMOR.

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WHEN a spontaneous cerebral hemorrhage occurs in a young adult without traumatic injury, hypertension or syphilis, a cerebral vascular tumor should be considered as a probable cause of the hemorrhage.

**Case Report.** L. H., a young negro, aged twenty-six years, was brought in an unconscious condition to the John Sealy Hospital at 9 A.M., July 29, 1925. His wife said he had been in perfect health. The morning of his death he went to his work at a filling station. While sitting in a chair he suddenly complained of a severe pain in his abdomen. He coughed a few times, vomited a small amount of greenish-yellow material, fainted and fell out of the chair. He was sent to the hospital immediately.

Examination showed a well-nourished, unconscious young negro. The temperature was 97.8° F., the respirations shallow and 24 per minute. The pulses were full, equal, synchronous, and easily compressible, 68 per minute. The blood pressure was 124 systolic and 72 diastolic. There was a soft blowing systolic murmur localized at the mitral area. The chest and abdomen were normal. The pupils were contracted and reacted slightly to light. Nuchal rigidity was present. The reflexes of the upper extremities were normal, those of the abdomen and lower extremities were absent. The signs of Hoffman, Babinski and Oppenheim could not be elicited. There was no ankle clonus. Kernig's sign was positive. There was no response to any stimulus. A catheterized specimen of urine showed a trace of sugar and many red blood cells. The white count was 14,200, of which 91 per cent were polymorphonuclear cells, 6 per cent were lymphocytes, 2 per cent transitionals and 1 per cent mononuclears. A spinal puncture revealed an increased pressure and a uniformly bloody fluid. The Wassermann reaction was subsequently reported negative.

By 3.30 P.M. the pupils had become dilated, the temperature was 102° F., the pulse was 88 and the respirations 30 per minute. During the withdrawal of the specimen of spinal fluid the pulse became very rapid and breathing stopped. The needle was immediately withdrawn. Attempt to revive the patient failed.

**Autopsy Report.** The body was that of a well-developed, well-nourished young negro with no evidence of external abnormality or injury. Scalp and skull were apparently normal. Some extravascular fluid blood was present in the piaarachnoid, chiefly about the base of the brain and over the cerebellum.

The brain was sectioned by Virchow's method. All four ventricles contained blood: In the third and lateral ventricles partly clotted, in the right less blood than in the left. In the anterior wall of the anterior cornu of the left lateral ventricle was a hemorrhagic tumor mass extending medially into the genu of the corpus callosum. Medirolaterally this mass measured 25 mm. and anteroposteriorly 15 mm.; it extended into the brain substance 12 mm., the deepest part to within 5 mm. of the cortical gray matter of the left gyrus rectus (Fig. 1). The overlying cortical surface was apparently normal. Attached to the ventricular surface of the tumor area was a large bloodclot. Section showed the tumor somewhat spongy and trabeculated, with blood filling the meshes of the tissue. The chorioid plexus showed nothing unusual. No definite evidence of compression of the brain into the foramen magnum was found.

Microscopic examination of the tumor showed numerous intercommunicating blood channels (Fig. 2), varying from a 2-mm. diameter down to capillary size. Several of these vessels contained blood, and some were filled with it. All had rather thick, well-formed walls. A single layer of swollen endothelial cells lined the vessels and there were scattered fibers of smooth muscle in the walls, many of which, especially in their outer adventitial portion, showed thickening and hyaline degeneration. No evidence of calcareous infiltration was seen. Several blood spaces were found just beneath the ependyma and some were ruptured and the overlying ependyma torn.

The stroma between the vessels was made up of glial tissue showing hemorrhagic infiltration near the area of ruptured vessels and toward the periphery of the tumor infiltration with edematous fluid, enough in some areas to form definite collections which pushed the glial tissue aside. We found nothing abnormal in the brain cortex.

Small atheromatous areas were found in the aorta, and small scars in the apices of both lungs with an associated localized fibrous pleurisy. Microscopically, the myocardium showed segmentation and fragmentation. The other organs and tissues showed nothing unusual.

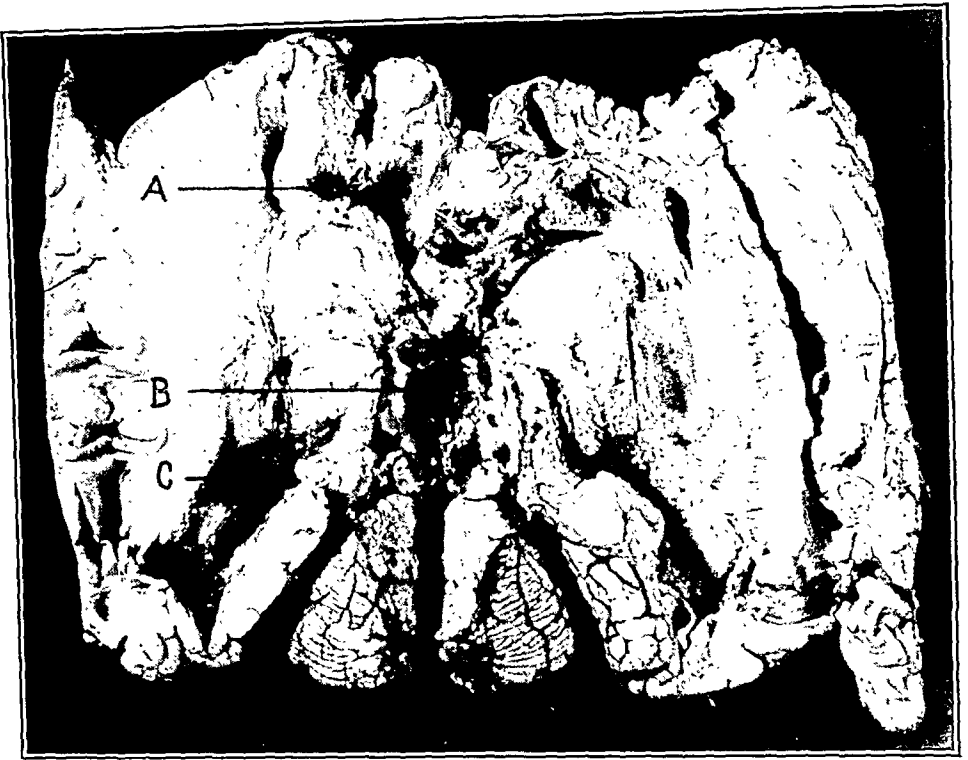


FIG. 1.—Hemorrhage into brain from vascular tumor: *A*, tumor area; *B*, hemorrhage into third ventricle; *C*, hemorrhage into left lateral ventricle.



FIG. 2.—Photomicrograph of vascular tumor shown in Fig. 1.



**Discussion.** The etiology of cerebral vascular tumors is unsettled. Trauma may be a factor (Pineas,<sup>1</sup> Sachs<sup>2</sup>). A congenital origin is a widely accepted explanation (Ewing,<sup>3</sup> MacCallum<sup>4</sup>). In support of this view is the fact that multiple lesions of a similar vascular nature have been found in the skin, brain and liver, etc. (Jaffé,<sup>5</sup> Dandy<sup>6</sup>). Several cases are on record showing angioma of the brain associated with vascular nevi of the skin (Sachs,<sup>2</sup> Strominger,<sup>7</sup> Hebold<sup>8</sup>). Hemangioma of the retina (von Hippel's disease) may be also found in conjunction with angiomatous cysts of the cerebellum (Lindau,<sup>9</sup> Cushing and Bailey<sup>10</sup>). Cobb<sup>11</sup> has reported a case of hemangioma of the spinal cord associated with nevi of the skin at the same segmental level. These observations have led some authors to believe that there is a developmental association between the central and the peripheral lesion. Lindau<sup>9</sup> has shown that these angioblastic tumors of the nervous system are to be found associated with cysts of the kidneys, cystic pancreas, and tumors of the adrenal glands.

There are in general two main groups of these blood-vessel tumors. In the first group there are new and proliferating blood-vessels, while in the second group one finds dilatation and metamorphosis of preëxisting vessels (Virchow,<sup>12</sup> Adami<sup>13</sup>). Some cases in the first group have been reported that have apparently come from remnants of angioblastic tissue, while other cases of this group have apparently come from preëxisting more fully developed vessels (Ribbert,<sup>14</sup> Moise,<sup>15</sup> Schley<sup>16</sup>). In this first group, there are new growths made up essentially of blood and blood-vessel elements. These are spoken of as angiomas.

In the second group, one finds both those cases which have resulted from dilatation of preëxisting more fully developed vessels, somewhat after the histio-mechanical laws of Thoma,<sup>17</sup> and also those cases resulting from dilatation and metamorphosis of certain embryological vessels which had failed to undergo normal regression (Moise<sup>15</sup>). The conditions of this second group are spoken of as either telangiectases or hamartomas (Albrecht<sup>18</sup>).

Angiomas grow. Both clinically and pathologically there may be evidence of their growth (Ewing<sup>3</sup>). One is able to find, at least in some portion of these tumors, vessel walls that are poorly developed, and usually lined with two or more layers of endothelial cells. These tumors may be represented by numerous blind vascular spaces which are entirely separated from the general circulation and in such cases the blood found in these spaces is formed through the hemoblastic activity of the cells lining the spaces (Ribbert,<sup>14</sup> Luschka,<sup>19</sup> MacCurdy<sup>20</sup>). Other angiomas are connected up with the systemic circulation through either a vein, an artery, or both vein and artery.

In telangiectases or hamartomas one finds the vessels increased in size, but there is little evidence of new vessel formation. These

vessels or vascular networks, are usually lined with a single layer of endothelium and may show thickening and degenerative changes in their walls. In our opinion, the case reported here is a telangiectasia.

Hemorrhage from vascular abnormalities in the body has been mentioned in the literature, but has not been sufficiently emphasized in relation to cerebral vascular tumors. Epistaxis is frequently seen in hereditary hemorrhagic telangiectases of the nasal and buccal membranes (Osler,<sup>21</sup> Hanes,<sup>22</sup> Steiner<sup>23</sup>). Hemorrhage from hemangiomas may be a cause of paraplegia (Sargent,<sup>24</sup> and others). Wirgman<sup>25</sup> has reported a case of a young man, aged twenty years, with a fatal intracranial hemorrhage from an angioma in the cerebellar peduncle, who thirty minutes before death had been in a cheerful mood and apparently well. Müller<sup>26</sup> has described a case of a young man, aged seventeen years, who had been sick for five days with headache, became comatose and developed ocular palsy and cervical rigidity before death. The autopsy showed that death was due to a hemorrhage from an angioma situated in the region of the caudate nucleus. Latham<sup>27</sup> has reported a case of a man, aged forty-four years, who had suffered from headache for three weeks and was suddenly seized with epileptic fits and became unconscious. Five days later he died, and necropsy revealed a hemorrhage from a cavernous hemangioma at the juncture of the right frontal lobe and precentral gyrus. Dandy<sup>6</sup> has reported a case in a man aged 30, who died suddenly while on the way to the operating room for relief of brain tumor symptoms. Postmortem examination showed a large hemorrhage into the occipital and temporal lobes, coming from a small angioma in the region of the angular gyrus.

**Summary and Conclusion.** A case of fatal intracranial hemorrhage from a cerebral vascular telangiectasia in a young man is reported, with autopsy findings, and brief review and discussion of the literature. A vascular tumor should be borne in mind as a possible source of intracranial hemorrhage, when such hemorrhage occurs in a previously healthy young adult.

NOTE.—For a more extensive consideration of the symptomatology, pathology and treatment the reader is referred to the writings of Sachs, Lindau, Dandy, Cushing and Bailey.

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## CEREBRAL HEMORRHAGE FROM VENOUS AND CAPILLARY STASIS.\*

### A REPORT OF FIVE CASES WITH AUTOPSY.

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THESE 5 cases are reported together because all showed hemorrhage into the brain substance from congested veins and capillaries.

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Etiologically the cases are not similar: of the 3 with thrombosis of the dural sinuses and pial veins 1 (Case I) followed pneumonia and phlebitis; another (Case II) resulted from purulent meningitis; the third (Case III) had an unsuspected pericarditis. The other 2 are patients who were asphyxiated, one by illuminating gas (Case IV) and the other at birth because of respiratory failure of the mother. In these 2 there is no question of infectious thrombosis of the veins or dural sinuses, but great stasis and congestion of the cranial veins is known to occur during asphyxia. This has been observed experimentally by Forbes and Wolff<sup>1,2</sup> and is a common clinical observation. From the clinical standpoint, the cases are similar in that all died after a prolonged period of unconsciousness, during which 4 of the patients had convulsions, while the fifth (Case IV) had muscular twitchings.

Interest in the vascular lesions of the brain has centered upon the arterial side of the circulation. Ever since the epoch-making work of Charcot and Bouchard the question of arterial cerebral hemorrhage has been intelligently investigated. Hemorrhage from the veins and capillaries of the brain, however, has received comparatively little attention. Judging from the small amount that has been written on this aspect of cerebral hemorrhage, such lesions might be considered either rare or of little importance. Lesions like those herein described are often designated as "hemorrhagic encephalitis." The observations on these 5 cases indicate that encephalitis, if present, acts on the bloodvessels merely by thrombosis. The hemorrhage apparently results from a mechanical obstruction to the venous circulation with its increased venous pressure plus anoxemia.

**Case Reports.** CASE I.—(N-27-73.) A WOMAN, AGED FORTY-SIX YEARS WITH A REMARKABLE FAMILY HISTORY OF PHLEBITIS. AFTER BRONCHOPNEUMONIA AN EXTENSIVE PHLEBITIS IN THE LEGS, ABDOMEN AND FINALLY IN THE VEINS OF THE DURA AND BRAIN. CONVULSIONS AND DEATH IN COMA. AUTOPSY: TREMENDOUS THROMBOSIS OF ILIAC VEINS UP TO VENA CAVA AND OF VENOUS SINUSES OF DURA. CONGESTION, HEMORRHAGE AND SOFTENING OF NUMEROUS AREAS IN THE BRAIN.

*Clinical History: Family History.* It is interesting to note in connection with the phlebitis reported below, that during three generations of the family, there have been 7 cases of very extensive phlebitis, most of which have proved fatal.

*Past History.* The patient was a woman, aged forty-six years, the mother of six children. Eighteen months previously, she fell from a horse and suffered a concussion of the brain. This was not followed by any apparent ill effects.

*Present Illness.* Following a month of fatigue while tending a daughter with pneumonia, the patient developed a fever of 105° F. On May 15, a physical examination showed cyanosis, pain over the upper right chest, definite râles at the apex and questionable consolidation of the right apex and base. The white blood count was 13,000; pulse, 100; blood pressure, 110 systolic and 80 diastolic; blood culture, negative. On May 19, the

condition was much the same; at this time a sputum culture showed Type IV pneumococci. A diagnosis of bronchopneumonia was made. On May 24 the pneumonia had spread to the left lung. On June 1 the patient complained of pain in her right thigh and said that she was going to have phlebitis; two days later phlebitis was present. Two weeks later phlebitis developed also in the left leg. On June 23, the bronchopneumonia was still present with phlebitis in both legs. At this time convulsive movements set in; these started in the left side of the mouth and then spread to the left forearm, hand and fingers. These unilateral convulsions came at intervals of two or three hours, later they became more frequent, and after about eighteen hours there was one convulsion on the right side and one general convulsion. A blood culture at this time was negative. On June 23, the patient lapsed into unconsciousness; this condition was maintained until her death on June 28.

**Summary of Autopsy Report.\*** *Lungs.* In the trachea, and bronchi of both lungs there is found a large quantity of purulent material. Through the branches of the pulmonary arteries there is extensive thrombosis, some of the branches apparently being completely occluded. There are extensive adhesions of both lungs to chest wall and diaphragm. The chief pathology of the lungs is in brief: bronchopneumonia, with chronic bronchitis, peribronchitis and bronchiectasis; alveolar emphysema; chronic fibrous pleuritis; pulmonary thrombosis.

*Spleen.* Acute splenic tumor.

*Liver.* Shows small, pale areas scattered through the liver, presumably caused by obliteration of the sinusoids by greatly swollen liver cells filled with glycogen vacuoles, such as are often found in individuals where death is due to cerebral traumatism.

*Heart, gall bladder, gastrointestinal tract, kidneys:* all essentially normal.

*Dissection of the Veins of the Abdomen and Legs.* Thrombophlebitis of both femoral veins, internal and external iliac veins and their tributaries. Thrombosis of the common iliac veins and inferior vena cava. Thrombosis of the ovarian veins and the veins of the vesical, vaginal and uterine plexuses.

*Middle Ears.* Normal.

*Sphenoidal Sinuses.* Both filled with a turbid, thick, mucoid material.

*Pituitary Gland.* Normal.

*Calvarium.* Careful examination (in view of the history of concussion) showed no evidence whatever of any traumatic injury to the bone.

*Sinuses of the Dura.* The posterior part of the superior longitudinal sinus is filled with a firm red clot which is continued through this toward and into the jugular foramina. From the midportion centrally in both lateral sinuses the clot is only partially occluding and is adherent to the external walls of the sinus. The cavernous sinuses on both sides are apparently free from clot.

*Brain. Examination of the Fresh Brain.* There is marked flattening of the convolutions on both sides. There is very marked discoloration of the surface of the brain on the right side involving the anterior and posterior central gyri and the posterior portion of the superior parietal lobe. On the left side, this discoloration involves the anterior and posterior central gyri only, but at this point the consistency of the brain is soft, almost fluctuant and an incision across the fissure of Rolando reveals a fairly large cavity, anterior to this sulcus, filled with a soft red brain substance and bloodclot. The central portions of both the precentral and postcentral gyri present opaque grayish areas thickly studded with minute hemorrhagic areas. On the right side, the same description applies both to motor gyri and to the

\* These first eleven paragraphs are a summary of an extensive report kindly given us by Prof. S. B. Wolbach, under the file No. H-27-890 at the Harvard Medical School.

region posteriorly situated. No further incisions were made. The base of the brain appears to be normal. Cerebellum, pons, and medulla are apparently normal externally. The arteries and veins at the base of the brain are normal in appearance. The brain was fixed in 10 per cent formalin and given to the Department of Neuropathology for further study.

*Examination of the Hardened Brain.* On frontal section through the frontal lobes about 4.5 cm. from the frontal poles, there is an oval hemorrhagic area, 1 by 0.5 cm. just lateral to the base of the left superior frontal sulcus, and 1 cm. from the surface. It involves chiefly the gray matter and shows many pin-point hemorrhages. There is a second darkened area in the left hemisphere at the same level; this is 1 by 1.5 cm. and lies in the white matter directly under the left superior frontal gyrus, and about 0.5 cm. from the midline. As already noted, when examining the fresh brain, the surface over these lesions shows dark, hardened, thrombosed vessels with perivascular extravasation of blood. The areas of softening, discoloration and petechial hemorrhage under the surface appear to be associated with the thrombosed vessels at the surface.

A second section (Fig. 1) cut 0.5 cm. posteriorly to the first section, passing through the anterior tip of the lateral ventricles and the genu of the corpus callosum, shows a continuation and enlargement of these two lesions. The more lateral area, now 2 by 1.5 cm. involves all of the gray matter at the base of the left superior frontal sulcus. Median to this lies the second area, 1.5 by 1 cm. and about 1 cm. from the midline. Although it lies 0.5 cm. from the surface, it is connected with the thrombosed vessels at the surface by darkened extravasated blood extending down into a small sulcus. The right side at this level is quite clear except for a very few pin-point hemorrhages in the white matter.

A third section cut more posteriorly passes through the anterior perforated substance, the temporal lobes and the anterior portion of the corpus striatum. On the left side between the superior and middle frontal convolutions, there is a wedged-shaped area 1.5 cm. long and 0.5 cm. wide of opaque jellylike, material which obliterates the fissure between the convolutions. In the left inferior frontal convolution, there is a grayish-green area 1 cm. below the surface and 1.5 by 1 cm. in size, the periphery of which is studded with minute pin-point hemorrhages of brownish color, and the center of which is necrotic and largely liquefied. This is later seen to be the anterior end of a large softening which extends backward and downward in the left hemisphere. The right side is normal except for a slight discoloration and a few pin-point hemorrhages in the superior frontal convolution. The superior sagittal sinus is filled with a dark-red clot.

The fourth section is made through the postcentral gyrus, and passes through the midthalamus, tail of the caudate nucleus, and the cerebral peduncles. This shows the superior sagittal sinus filled with thrombus, the center of which is gray, becoming progressively browner as the periphery is approached. On the left side, there is a cavity communicating with the subdural space which gapes widely and extends deeply into the white matter for 5 cm. This opening (incision) was made at the time of the autopsy. About 1 cm. medianward from the opening, there is another greenish area with many punctate hemorrhages, in size 1.5 by 0.5 cm. About 1.5 cm. medianward to this, with its apex downward, there is a blunt triangle about 2 cm. in width involving the superior portion of the paracentral gyri; this has similar color changes and many pin-point hemorrhages. In the right postcentral gyrus about 3 cm. from the midline, there is an area of greenish-yellow tissue 2.5 by 2.5 cm. surrounded by many pin-point hemorrhages. These areas of discoloration and hemorrhage appear to be associated with thrombosed vessels on the surface, as do the areas seen in sections already described.

A fifth section (Fig. 2) passes through the parietal lobes, splenium of the corpus callosum, cerebellum and pons. The left side shows the cavity wider but not so deep. (In the accompanying figure, the cavity appears greater than it really is due to the incision made at autopsy.) The walls of the cavity are covered with grayish-green necrotic material. The medial wall consists of a reddish-stained area extending from the external surface about 1.5 cm. deep and 1.5 cm. from the midline. The lateral wall of the cavity extends from the aperture downward into the middle of the white matter underlying the inferior parietal convolution, and thence medially to within 2 cm. of the midline. The superior sagittal sinus is completely filled with thrombus which is grayish and very firm. The right hemisphere shows a triangular greenish-yellow area in the white matter, this area extends upward toward the cortex where there appear innumerable pin-point hemorrhages, the whole area being about 1 by 2.5 cm.

The next section, through the middle of the precuneus and cerebellum, shows the superior sagittal sinus still thrombosed completely: the inferior sagittal sinus is not only patent but empty. On the left is a round area 2.5 cm. from the midline just subjacent to the gray matter, greenish in color and 1.5 by 1.5 cm. in size. On the right side, similarly placed is a larger softened and hemorrhagic area which extends to the surface. Just beneath it, but separate is another spot about the size of a pea. All three present the characteristic pin-point hemorrhages described above.

A cut through the occipital lobes presents much the same picture, the lesions on both sides extending backward into the cuneate gyri.

The cerebellum and brain stem present no apparent gross abnormality.

*Summary.* The brain presents two large areas of softening (see Fig. 2a for diagrammatic location), of which that in the left hemisphere is the larger, beginning about 1.75 cm. below the cortex of the operculum of the inferior frontal convolution and extending backward toward the occiput to become, in the paracentral region, a cavity of approximately 20 cc. volume; this ruptured and opened on to the surface of the brain at autopsy. As the lesion proceeds backward the cavity reaches within 1.5 cm. of the body of the left lateral ventricle. The posterior aspect of the cavity ends just posterior to the ramus lateralis of the sulcus cinguli, whence the softening continues as a narrow area beneath the superior parietal lobe to the middle of the precuneus. On the right side, a roughly spindle-shaped softening begins 5 cm. from the frontal pole in the superior frontal convolution and proceeds backward; its largest portion is in the paracentral region; posteriorly it tapers off to end in the precuneus. Several small hemorrhagic areas are directly contiguous with the two main lesions.

*Microscopic Examination of the Brain.* Sections for microscopic study were taken from the superior sagittal sinus, and from two different parts of the left superior frontal gyrus. These were stained: *a*, with hematoxylin and eosin; *b*, with Spielmeyer's myelin sheath stain.

The section through the superior sagittal sinus shows a thrombosed vessel. There is nothing particularly unusual, the thrombosis being the usual picture in which organization has taken place around the periphery and is working in toward the center, the center being somewhat canalized. The tissue around the vessel is filled with blood clot which is speckled with dark pigment much of which has been ingested by phagocytic cells.

The sections through the cortex show many pial vessels thrombosed, some showing organized thrombi. Where these sections have cut across a sulcus, a thrombosed vein may be seen extending into the depths of the sulcus. These, too, are surrounded with dark pigment, much of which has been ingested by phagocytic cells. The brain substance itself shows many areas of hemorrhage. In certain areas the hemorrhage is present most abundantly in the gray matter; in other places the white matter is chiefly involved;

some of the hemorrhagic areas extend into both white and gray matter. These areas are of various sizes; they are congested and edematous and are made up of clusters of small capillary extravasations. These are mostly circular and many have the appearance of a ring around a central cluster of large mononuclear cells, many of which have ingested red blood cells or pigment. Occasionally a bloodvessel may be seen within one of these areas of hemorrhage, but generally the hemorrhage is so dense that all underlying structure is obscured. Many of the vessels which are seen in the substance of the brain are thrombosed, this is true not only of the larger vessels, but also of the smaller branches.

Fig. 3 shows various points of interest that seem to explain the mechanism of the petechial hemorrhages. Beyond the limits of the photograph (to the left and upward) there is a thrombosed vessel, completely occluded and partially organized on the surface in the pia. This can be followed as it runs along the sulcus deeply into the brain substance where it shows across the upper part of Fig. 3. The sulcus is filled with a clot. In the gray matter near the sulcus (S) there is a little hemorrhage, but considerable edema. At a deeper level there is abundant hemorrhage which involves chiefly the gray matter bordering the sulcus, but which extends slightly into the white matter. Many of the hemorrhages in the proximity of the sulcus appear as streaks, this is because there has been much diapedesis from these small vessels; their walls appear to be much damaged and many of the vessels are traceable only as streaks of free red blood cells. Further out from the sulcus, the areas of hemorrhage are more circular and considerably larger. The hemorrhage is limited mostly to the lower side of the sulcus, above there is merely congestion of the capillaries and larger vessels, such as is seen in the area where gray matter merges into white (x). This is between the mass of linear and confluent extravasations in the gray matter and the more spherical hemorrhages in the white matter (W).

In a final note on the autopsy Professor Wolbach says: "In spite of the failure to obtain growth from the cultures and to demonstrate evidence in the histologic study, the extensive thrombosis of veins and cerebral sinuses must have been initiated by an infectious process localized in the vein in probably more than one situation. I have seen similar conditions in typhoid fever and in typhus.

"The lungs give positive evidence of a long continued bronchitis, persisting from a bronchopneumonia which, because of the peribronchial and interstitial pneumonitis, was probably streptococcal, possibly influenzal (*Bacillus influenzae*) in origin. The lungs would seem to have been the most probable source of blood-stream invasion leading to the thrombosis inasmuch as thrombosis of pulmonary veins (not found in the present case) is not infrequent in the present type of lung infection.

"There is no histologic evidence of peculiarity of the veins in this case; on the other hand, there is abundant evidence of normal sequences taking place in the processes of repair, in organization, canalization and establishment of collateral routes as seen in the tissues surrounding the veins selected for study.

"The cause of death was cerebral softening due to the extensive blocking of venous routes from the brain."

CASE II.—(N-21-239.) GIRL, AGED TWO AND A QUARTER YEARS, WITH OTITIS AND MENINGITIS FOR THREE WEEKS, CONVULSIONS THREE DAYS, COMA AND DEATH. AUTOPSY: THROMBOSIS OF PIAL VEINS AND CONGESTION, HEMORRHAGE, SOFTENING AND ABSCESS IN UNDERLYING BRAIN TISSUE.

*Clinical History.* A girl, aged two and a quarter years, was admitted to the Children's Hospital on December 6, 1921. The illness was of three

weeks' duration, beginning with a stiff neck and poor appetite. About a week later, there had been vomiting and a discharge from the right ear. She became increasingly ill, later developing a slight cough. Three days before death she began to have irregular jerking and twitching of the mouth, arms and legs.

Physical examination at this time showed a prostrated and sick-looking child, who noticed nothing that was going on. There was a thick mucoid purulent discharge from the right ear. Moist râles were heard throughout the chest. The neck was held stiffly and movement caused pain. There were frequent spasms which involved the right side of the face, but in which the motor division of the fifth nerve did not take part. There were general spasms of the body which were marked by an extensor rigidity of the left arm and leg, and a flexor rigidity of the right arm and leg. The corneal reflex on the right was absent. The eye grounds were normal. The blood Wassermann was positive; red blood cells, 2,900,000; white blood cells, 12,700; hemoglobin, 50 per cent. Lumbar puncture showed a clear fluid under slightly increased pressure with 30 white cells per c.mm. and 18 red cells. Just before death the spinal fluid became opalescent, the pressure increased, the white cell count was then 320 per c.mm.

*Autopsy Findings.* The pleural cavities, pericardial cavity, heart, spleen, gastrointestinal tract, pancreas, kidneys, adrenal, aorta and genitalia were all essentially normal. The lungs showed bronchitis, peribronchitis, areas of bronchopneumonia and a pulmonary infarct in the left lower lobe. The liver showed a small amount of central necrosis and fatty infiltration.

Gross examination of the brain showed thrombosis of the sinuses and cortical veins. The superior longitudinal sinus is engorged, bulging, and very firm to the touch. On opening it, it is seen to be completely thrombosed. Both lateral sinuses are prominent, and, with the inferior petrosal sinus, are found to contain thrombi. The jugular veins are not thrombosed. Many pial veins are thrombosed, they are bulging, reddish black in color and firm in consistency (Fig. 4).

Extending over the superior aspect of the parietal lobes, there is a purulent exudate. This is thickest along the course of the veins, but is found also lying in the sulci and to a less extent spread over the cortex. The exudate is limited in area to the superior aspect of the parietal lobes, and the frontal and occipital poles. The base of the brain is free from exudate.

There are numerous small punctate reddish-black hemorrhagic areas on the surface of the cortex in the posterior half of both frontal lobes superiorly, and practically over the whole of the superior surface of both parietal lobes. The left lateral hemisphere is larger than the right and gives a definite fluctuating sensation to palpation. The cranial nerves, cerebral arteries, and entire base of the brain are normal except for the presence of a pressure cone on the under surface of the cerebellum.

On making frontal sections through the brain, hardened in formalin, from before backward the following points are noticed. In the anterior portion of the frontal lobes there is blood in the sulci and numerous fine dark-red punctate hemorrhages throughout the gray and white matter; one ecchymotic patch about 2 cm. in diameter is confined almost entirely to the gray matter of the middle frontal gyrus. On sectioning through the right middle frontal gyrus there is found a cavitation containing blood and pus. This measures vertically 2 cm. and from 4 to 8 cm. transversely (Fig. 5). It is surrounded by punctate hemorrhages of varying size and the white matter adjoining it is of a dirty yellow color; on the left side the sulci are engorged with blood; the gray matter adjacent to them is of a reddish color, bordered by punctate hemorrhages in the white and gray matter. The next section, through the fissure of Rolando, reveals a practically normal condition in the right frontal lobe, while on the left there are extensive punctate and also

fairly large hemorrhages in both white and gray matter. Extending obliquely into the insula from the midportion of the corona radiata there is an irregularly shaped necrotic, ragged abscess measuring 2.5 by 1.5 by 1 cm. in the central portion of the left parietal lobe. Directly opposite to the posterior horn of this cavity, there is an extensive brownish discoloration of the globus pallidus, claustrum, external capsule, caudate nucleus, and superior fibers of the internal capsule. A section directly through the splenium of the corpus callosum and cutting the cerebellum shows discrete and confluent punctate hemorrhages in the gray and white matter of the parietal lobes for a distance of about 5 cm. lateral to the longitudinal fissure, somewhat more extensive on the left side. Finally, a section through the occipital lobe shows the same condition to a very slight degree, and also a small amount of blood in some of the sulci.

The brain stem and cerebellum are essentially normal.

*Microscopic Examination of the Brain.* Sections through the cortex show three main lesions: (1) thrombosis of the cortical vessels (Fig. 6); not only are the surface vessels thrombosed, but also thrombi may be found in the smaller branches which extend down into the brain substance. The large surface thromboses are definitely organized; some of the smaller, deep thrombi are likewise organized. The veins that are not occluded are greatly congested and many show extravasation of red cells.

2. There is a purulent exudate over the surface; this infiltrates the pia arachnoid; it consists mostly of polymorphonuclear leukocytes, but there are also some mononuclears present. Leukocytes may also be found in abundance in the bloodvessels.

3. There are circumscribed areas of hemorrhage of variable size throughout the white and the gray matter. Scattered through these are scavenger cells and numerous polymorphonuclear leukocytes most of which are in a poor state of preservation. In these areas, there is marked congestion and edema. The normal nerve cells have completely disappeared; the glia cells are separated by vacuolated, lacelike, edematous spaces (Fig. 7). The more solid areas which stand out as islands in the softer edematous tissue show a striking congestion and capillary injection. All the capillaries in such areas are engorged with red blood cells and hence stand out conspicuously from the surrounding tissue. Occasionally one of these is found to terminate in a cluster of red blood cells which were apparently showered into the surrounding tissue by the ruptured capillary.

**CASE III.—(N-28-25.) GIRL AGED FOURTEEN MONTHS WITH SUDDEN ONSET OF VOMITING AND TWO DAYS LATER UNILATERAL CONVULSIONS. DEATH ON FOURTH DAY. AUTOPSY: PERICARDITIS, ARACHNOID HEMORRHAGE, THROMBOSIS OF SUPERIOR SAGITTAL SINUS, CONGESTION, EDEMA AND HEMORRHAGE OF SMALL AREAS OF UNDERLYING BRAIN.**

*Clinical History.* A child, aged fourteen months, was seen at home in status epilepticus. The past history was unimportant except for a short attack of fever four and a half months previously with vomiting.

The present illness began with a recurrence of the vomiting; milk and lime water were given, but the vomiting continued. The temperature at this time was 99.4° F. Two days later, physical examination showed a well-developed child with no abnormal physical signs. The neck was not stiff. On the fourth day, after the vomiting had somewhat abated, convulsions began. These involved the right side, including face, arm and leg. At this time the child became unconscious. Examination of the right retina showed three hemorrhages. The rectal temperature was now 102° F. The child was taken to the hospital about twelve hours before she died. Lumbar puncture was performed. Thirty cubic centimeters 50 per cent

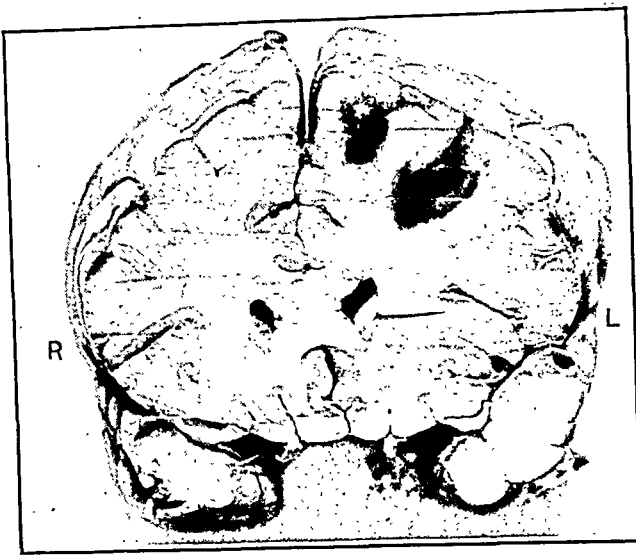


FIG. 1.—Section through anterior tip of lateral ventricles and genu of corpus callosum showing in the left hemisphere two areas of multiple minute hemorrhage with discoloration and softening at their centers. The upper lesion is seen to connect with the surface of the brain by a sulcus which contains a thrombosed vein.



FIG. 2.—Frontal section through splenium of corpus callosum, cerebellum and pons. The large area of softening and hemorrhage (left) is exaggerated by a cut (*C*) made at autopsy to promote hardening. The sinus (*S*) is seen to be filled with thrombus. At "*V*" are indicated three small thrombosed veins in the pia; a typical area of petechial hemorrhage with slight softening underlies these.

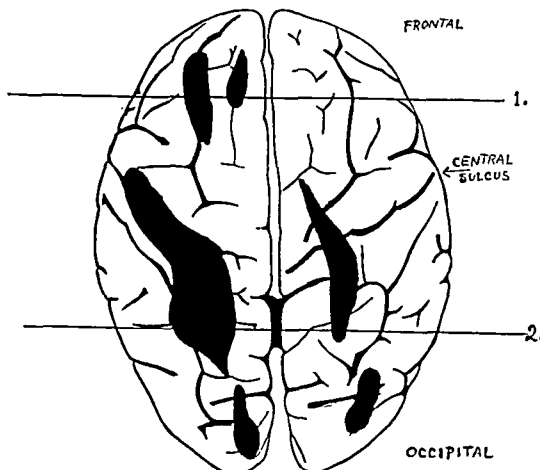


FIG. 2a.—Diagram showing location of main lesions in black. These lie deep in the brain as is seen from Figs. 1 and 2. The levels of the sections from which figures were made are indicated on the chart at "1" and "2."



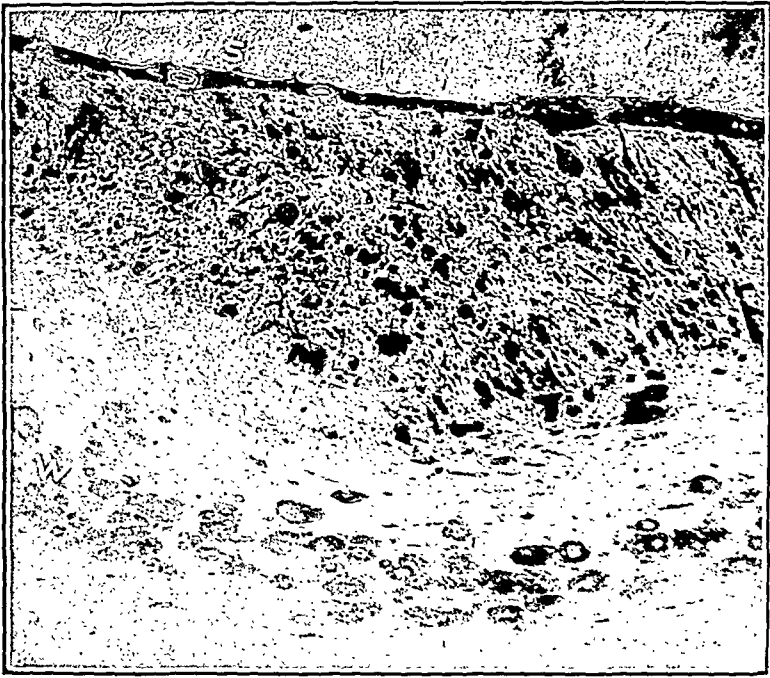


FIG. 3.—Low-power photomicrograph of area of multiple petechial hemorrhage near a thrombosed vein in a deep sulcus. For description see text.

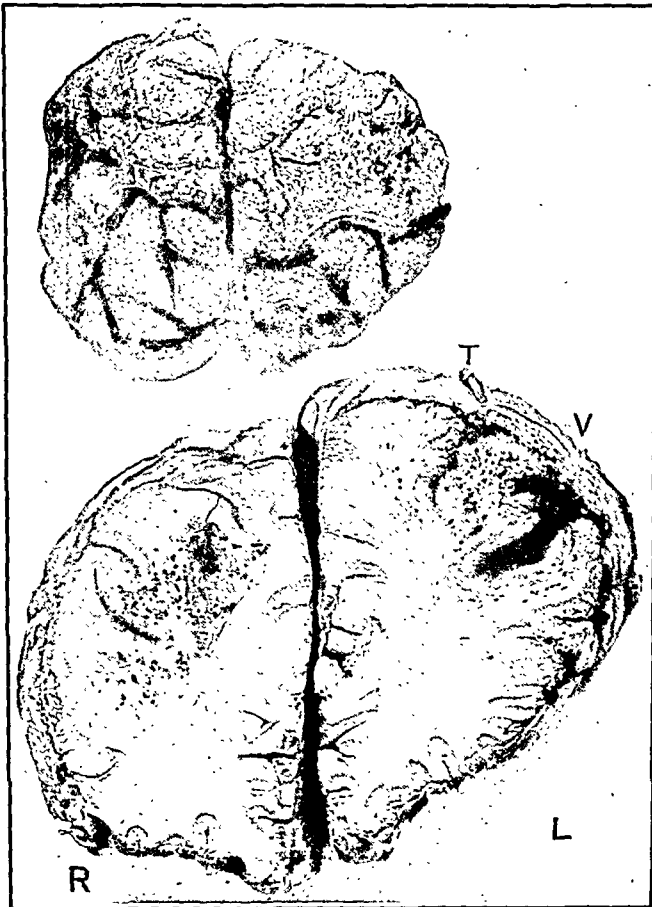


Fig. 4

Fig. 5

FIG. 4.—(Case II.) Surface of the frontal lobes showing meningitis and prominent thrombosed veins.

FIG. 5.—(Case II.) Frontal section through frontal lobes. In the white matter of the right hemisphere is an abscess cavity surrounded by punctate hemorrhages. In the left hemisphere is a hemorrhagic and softened area subjacent to thrombosed veins on the surface. One of these (V) is surrounded by frank hemorrhage, another (T) is seen distended with clot on the surface and filled with organized clot on section.

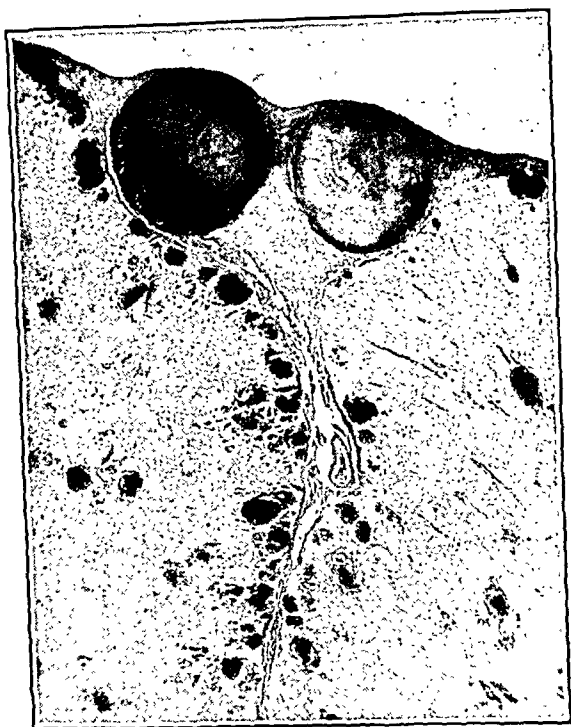


FIG. 6.—(Case II.) (Low-power photomicrograph.) Two large pial veins are seen filled with thrombus and surrounded by exudate. Along the sulcus beneath are many smaller veins greatly congested, some show the extravasation which makes the petechial hemorrhages.

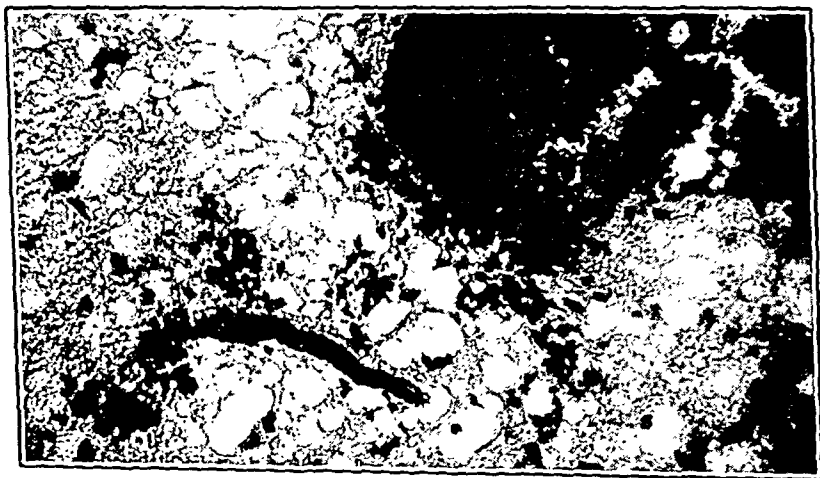


FIG. 7.—(Case II.) (High-power photomicrograph.) In the upper right-hand corner is a hemorrhage; the tissue about this is softened and edematous. In the lower left is seen a distended capillary the left end of which has ruptured and caused a minute hemorrhage.

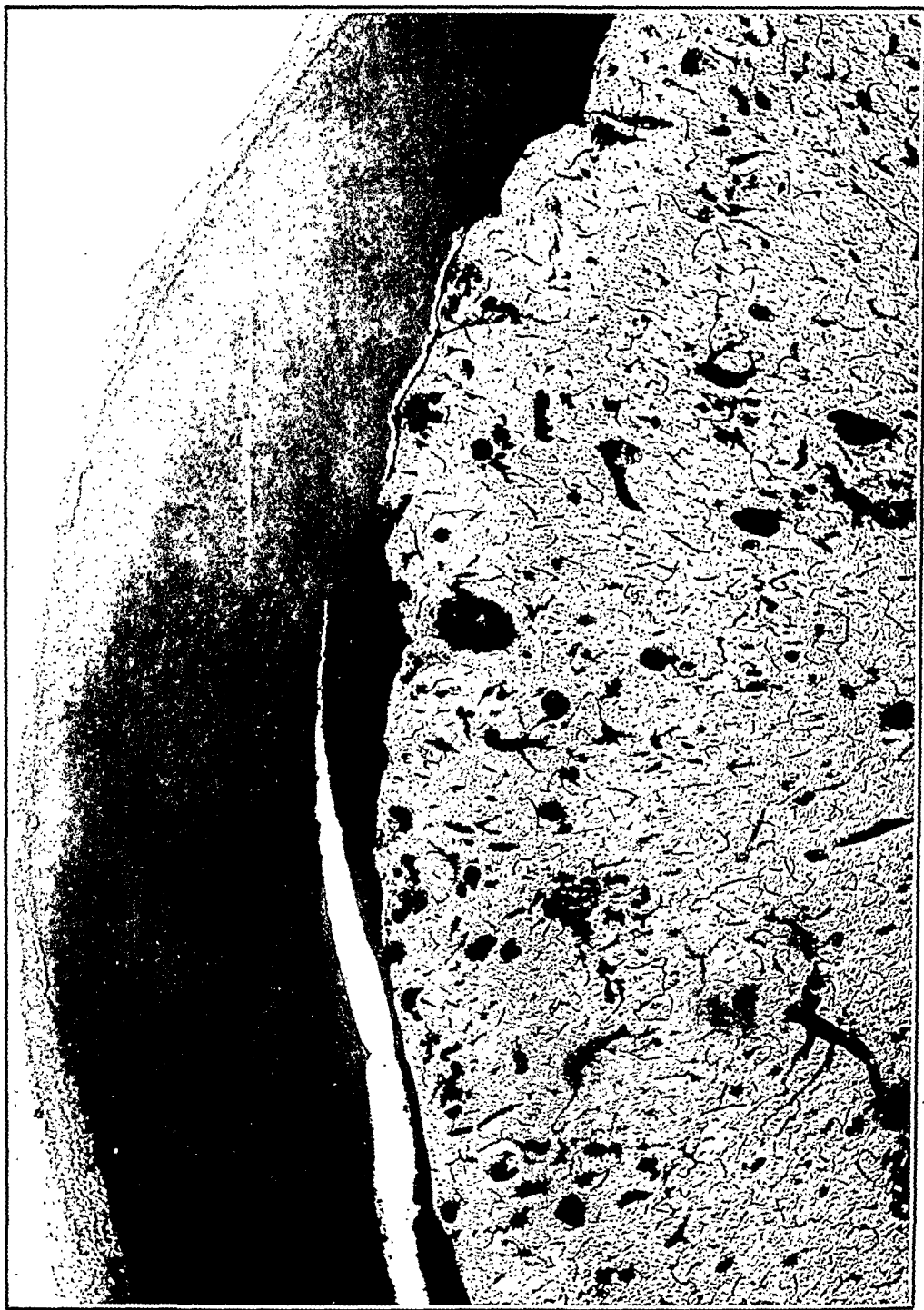


FIG. 8.—(Case III.) Subarachnoid hemorrhage (*H*) lifting up the outer arachnoid membrane (*A*) and compressing the pial veins. In the cortex (*C*) all the vessels are greatly congested. Many of them have extravasated red cells about them; a few have ruptured and caused punctate hemorrhages.

*A*

*H*

*C*

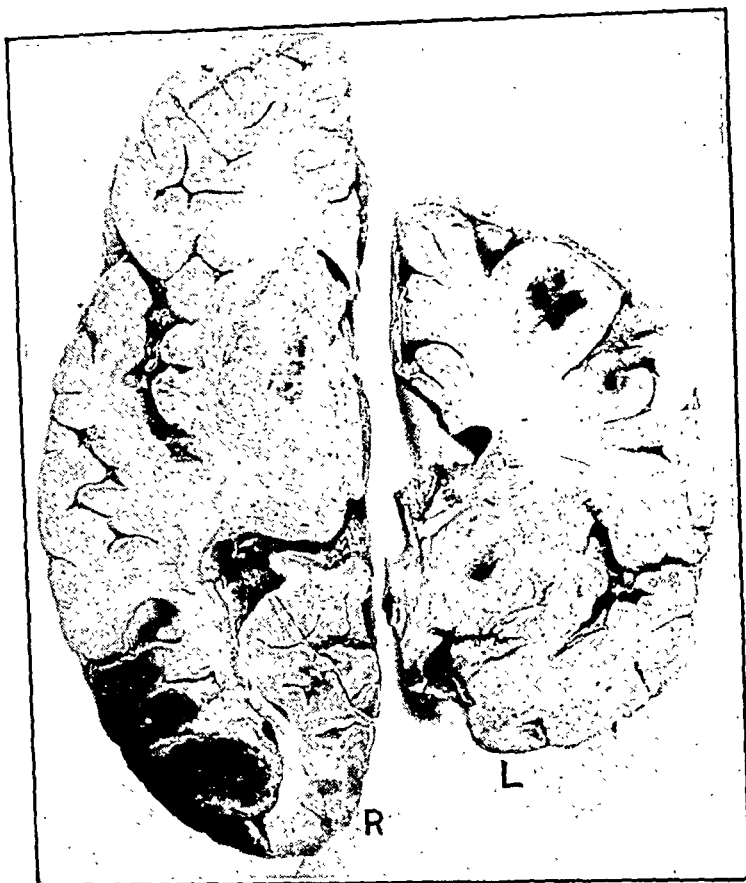


FIG. 9.—(Case IV.) The horizontal section of the right hemisphere (*R*) shows an area of softening with discoloration and hemorrhage in the globus pallidus of the lenticular nucleus. In the cortex of the occipital lobe is an extensive hemorrhagic area, the periphery of this is made up of discrete minute hemorrhages, which in the center are confluent and softened. A vertical frontal section of the left hemisphere (*L*) shows one of the many small hemorrhagic areas in the cortex; there is also a small lesion in the globus pallidus similar to that in the right hemisphere.



FIG. 10.—(Case IV.) (Low-power photomicrograph.) Small group of petechial hemorrhages in cortex, grouped about one sulcus as if dependent upon one venous outlet. The lesion is most marked in the gray matter but extends into the less vascular white. There is little blood in the arachnoid space.

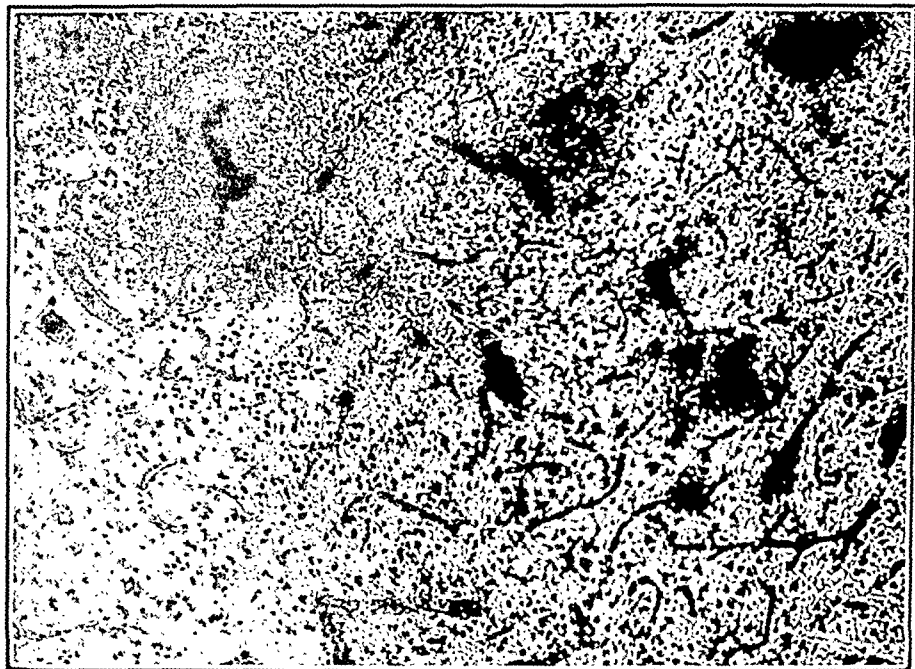


FIG. 11.—(Case IV.) (High-power photomicrograph.) This is an enlargement of a small area from Fig. 10. There is great congestion of the bloodvessels with occasional rupture and hemorrhage. The lower left-hand part is white matter, the upper and right-hand two-thirds is gray; the greater vascular supply and more numerous hemorrhages in the gray matter are obvious.



FIG. 12.—(Case V.) (Low-power photomicrograph.) Congestion of the choroid plexus with some extravasation of red cells into the interstitial spaces. (Morgan stain.)

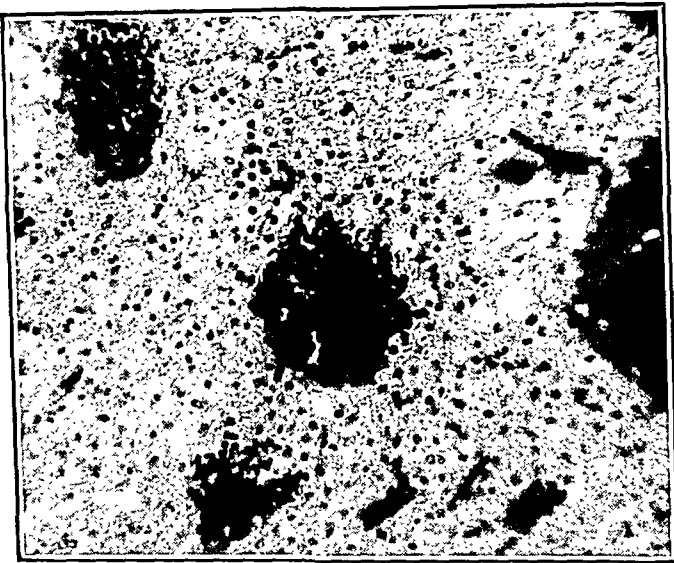


FIG. 13.—(Case V.) (High-power photomicrograph.) Section through the medulla showing great congestion of veins and capillaries with slight infiltration of the red cells out into the surrounding tissue. (Morgan stain.)



glucose were injected intravenously. The temperature rose to 108° F. As the child was dying a ventricular puncture was performed.

*Summary of Autopsy Report.* The only significant lesion found in the general viscera was an organized pericarditis, for which there was no apparent cause. The lungs showed a slight congestion; the liver slight congestion and some fatty infiltration; the cortex of the adrenal was unusually narrow. The important changes were found in the brain.

*Brain: Gross Findings.* The dura was normal except for a single needle puncture on the right side of the fontanel. There was no free blood in the subdural space. The pia-arachnoid space on the left was distended with a recent, diffuse extravasation of blood. The superior sagittal sinus, straight sinus, and portions of the lateral sinuses were distended with clotted blood which was deep maroon in color, firm, friable, suggesting antemortem thrombosis. The large superficial cerebral veins were distended like firm cords over the cerebral hemispheres on both sides. The capillaries were but little injected. The brain was normal in size and contour, and felt homogeneously soft. The convolutions on the right side were slightly flattened and the sulci slightly obliterated. The convolutions on the left were completely obscured by the blood in the arachnoid space. The vessels at the base were normal.

After twenty-four-hours' fixation in formalin, it was noted that the brain had a distinctly different appearance to that of the fresh state described above. The convolutions on the left were now apparent as very much enlarged and flattened gyri with obliterated sulci. The whole of the left hemisphere was now soft and semifluctuant as compared with the right which was of normal consistency.

On making frontal sections of the hardened brain, the extent and character of the hemorrhage is seen to better advantage. As noted at autopsy, it is limited to the left side. The sections show further that it is limited to the frontal and parietal lobes. The surface of the left temporal lobe is somewhat discolored, but shows no true hemorrhage. The hemorrhage consists of a very dark, hardened clot, which lies in the arachnoid, raising this membrane up from its normal position on the surface of the cortex. The clot extends into the sulci, widening them and compressing the cortex. The gray matter in these regions is discolored, giving a dark reddish-gray appearance through which may be seen small pin-point hemorrhages. The clot has distended the lateral fissure (of Sylvius) with extensive hemorrhage around the insula; it distends all the sulci of the parietal lobe; it extends into the longitudinal fissure and thence into the sulcus cinguli.

In a more anterior section, which cuts through the genu of the corpus callosum, and through the anterior portion of the basal ganglia the extent and character of the hemorrhage is much the same: limited to the frontal lobe, extending into the sulci, and compressing the discolored gray matter. In addition, this section shows a large clot widely distending the central sulcus and encroaching extensively into the cortex of the inferior portion of the precentral gyrus. Here the gray matter not only shows the discoloration noticed elsewhere, but is damaged by petechial hemorrhages and softening.

There is another distinct lesion running through the more anterior portion of the corpus callosum on the left. This dark oval area is due to the ventricular puncture performed at the time of death.

*Brain: Microscopic Examination.* A section cut from the superior sagittal sinus, shows bloodvessels congested and filled with blood cells. There is partial thrombosis. Throughout the thrombi of the sinuses there are numerous mononuclear leukocytes containing phagocytosed hemosiderin. In the dura itself there are a few foci of polymorphonuclear leukocytes.

Microscopic sections were made from the superior frontal gyrus, the



conspicuous feature of these sections are, first, of course, the subarachnoid hemorrhage, and second, a great congestion of all the bloodvessels in the cortex beneath (Fig. 8). The bloodclot at the surface shows no unusual features. It is very dense, extends into the sulci wherever possible, and all through it are numerous phagocytic cells which have taken up hemosiderin.

All the vessels of the gray matter, the larger branches and the small capillaries, are distended with blood, making the vessels stand out very prominently. Occasionally a vessel may be found which has begun to thrombose. There are diffuse perivascular hemorrhages; around the larger vessels they may be quite large, and around the capillaries they may be minute, consisting of a cluster of blood cells which appear to have escaped from a ruptured capillary. As in the large surface hemorrhage, there may be found in these smaller hemorrhages numerous phagocytic cells containing ingested pigment.

There is also edema in the gray matter.

The lesion in the corpus callosum, which was noticed in the gross sections, shows an area in which the myelinated fibers of the corpus callosum have undergone degeneration. The area has rather a homogeneous pinkish aspect. Throughout it are numerous scavenger cells which have phagocytized particles of the degenerated myelin. It is rather striking that there should be phagocytic reaction in view of the fact that the injury was made at the time of death.

CASE IV.—(N-28-18.) WOMAN, AGED EIGHTY-SIX YEARS, ASPHYXIATED WITH ILLUMINATING GAS, ARTERIOSCLEROSIS AND PARALYSIS OF ARM, UNCONSCIOUS, LIVED THREE DAYS. AUTOPSY: CALCIFICATION OF ARTERIES, MARKED ACUTE HYPEREMIA OF ALL ORGANS, NUMEROUS HEMORRHAGES ON PIAL SURFACE OF BRAIN AS WELL AS IN THE GRAY AND WHITE MATTER OF THE CORTEX. SMALL AREA OF SOFTENING AND HEMORRHAGE IN EACH GLOBUS PALLIDUS. CORTICAL HEMORRHAGES MADE UP OF NUMEROUS SMALL PUNCTATE EXTRAVASATIONS COALESCING. CHRONIC DEGENERATIVE CHANGES IN BASAL GANGLIA.

*Clinical History.* The patient, white woman, aged eighty-six years, was found in a room filled with illuminating gas. On entrance to the Boston City Hospital, there was a strong odor of gas on her breath; the respiration was deep and labored, all accessory muscles being brought into use. The rate was rapid. There was a flaccid paralysis of the right face and a spastic paralysis of both arms, more marked in the left than the right. Myoclonic twitching of the arms and legs occurred frequently. All the reflexes were hyperactive. The lungs were emphysematous with many râles. Heart not enlarged to percussion. Rate, 120; blood pressure, 111 systolic and 75 diastolic. There was slight pitting edema of the legs. Diagnosis was made of gas inhalation, senility, arteriosclerosis, myocardial insufficiency, and cerebral vascular accident with paralysis. The patient was given oxygen inhalation for twenty minutes with no effect on the breathing. Caffeine, adrenalin, and intravenous digalen strengthened and slowed the pulse, and caused less labored breathing. The patient did not regain consciousness from the time she was found until her death three days later.

*Summary of Autopsy Findings by Professor Leary:* *Heart.* The mitral orifice is slightly calcified. Slight hyperplasia of the left ventricle. The right heart is considerably dilated. The coronaries show calcification.

*Lungs.* Acute passive hyperemia.

*Liver.* Acute passive hyperemia.

*Gall Bladder.* Cholelithiasis.

*Genitalia.* General senility with periovaritis, perisalpingitis and bilateral hydrosalpinx.

*Kidneys.* Chronic progressive vascular nephritis. There was a universal acute passive hyperemia, and considerable arteriosclerosis, although this was not greater than might be expected in an individual of this age.

*Brain.* Examined in the Department of Neuropathology, after hardening in 10 per cent formalin. The meninges are quite normal; they strip off freely from all parts of the brain except over areas of hemorrhage in the cortex. The size of the brain appears to be normal. The convolutions are not flattened. All of the vessels appear more prominent and dilated than usual, and are quite pink in color. The middle cerebral arteries show regions of opacity with beginning calcification.

The conspicuous feature is the presence of several areas of hemorrhagic softening (Fig. 9) which on palpation in the fresh state showed some fluctuation. These areas do not project above the surface of the cortex; there is no arachnoid hemorrhage, the hemorrhage is limited entirely to the substance of the cortex itself. One of these areas lies 3.5 cm. from the anterior pole of the right hemisphere and 2.5 cm. from the midline; this is oval in shape, 3.5 cm. in width, and 5 cm. in length. There is a similar area over the occipital pole of the right hemisphere; this is 5.5 cm. in width.

On sectioning the right hemisphere, the necrotic area in the frontal region is found to extend to a depth of 1.5 cm. It is pyramidal in shape, with the base at the surface. The large necrotic area at the occipital pole extends into the white matter to a depth of 2.5 cm. from the surface of the cortex. Throughout the cut surfaces, minute areas of perivascular hemorrhage and necrosis can be seen. The largest of these, about 1 cm. long is situated in the basal ganglia and has largely destroyed the globus pallidus.

In the left hemisphere, similar areas of softening are found. Over the anterior pole there are small rather diffuse areas. A somewhat larger area involves a small region both in the postcentral and precentral gyri. The largest area is in the occipital lobe and is about 3 by 4.5 cm. The sulci in this hemisphere appear wider than those in the right hemisphere, especially in the anterior pole.

On sectioning the left hemisphere, minute areas of perivascular hemorrhage appear as they did in the right hemisphere. A large area extends through the gray matter of the cortex from the region of the precentral gyrus to the large necrotic area in the occipital lobe. Again there is an area of necrosis in the globus pallidus (Fig. 9).

Except for minute areas of perivascular hemorrhage and injection of the vessels, the midbrain, cerebellum and hind brain show no gross lesions.

*Microscopic Examination of the Brain.* Turning to a study of the microscopic preparations of the brain lesions, a very interesting picture is found in a section through the comparatively slight hemorrhage, mentioned above, found in the globus pallidus. Here there is apparently a two-fold lesion: an old chronic vascular disease which undoubtedly antedates the carbon monoxide poisoning; and the more direct results of the hemorrhage and the reaction to it. There is marked thickening and hardening of the vessels. They stand out as darkly-staining rings, which on closer inspection are seen to be composed of hyaline droplets in the walls of the vessels. This condition of the vessels is limited to the globus pallidus, which is also the limit of the area of hemorrhage in this region. In the globus pallidus there are no normal nerve cells; the glia cells are abundant, but many of these too have undergone partial necrosis. The hemorrhagic process in this area is less clear than in sections of the cortex to be described below, but here, too, there are found capillaries congested and distended with blood cells; occasionally one may be found that has just ruptured. There is a pronounced reaction to this hemorrhage; especially prominent are the great number of scavenger cells, some of which have taken up pigment from the red cells. Also there are to be found numerous "mulberry bodies" in the

pallidum and many corpora amylacea beneath the pia. Cloudy bluish areas of degeneration are seen which may be regarded as "mucoid degeneration"<sup>3</sup> an early stage of these same "mulberry bodies" or corpora amylacea.

A section made from one of the hemorrhages in the cortex of the occipital lobe is illustrated in the accompanying photograph (Fig. 10). Here the vascular disease of the vessels (which was seen to be a striking feature of the condition in the globus pallidus) is not present. The area of hemorrhage is sharply marked off. It is definitely pyramidal in shape and involves mostly the gray matter. The normal nerve cells have completely disappeared, while glia cells are abundant. The most prominent feature is the marked congestion (Fig. 11). All the capillaries are packed with red cells. Quite frequently small capillaries, or sometimes somewhat larger vessels, may be seen to have ruptured. Some may be found where the rupture is very small and only a few blood cells have escaped, while others are seen around which there is a greater collection of red cells. The reaction to the hemorrhage is less marked than in the globus pallidus. There are scavenger cells, some with phagocytized particles and pigment as before, but they are not numerous. The whole picture is that of acute congestion with diapedesis of red cells, small extravasations, and small hemorrhages from capillaries and veins.

**CASE V.—(N-29-1.)** INFANT ONE DAY OLD. PROLONGED ASPHYXIA, CONVULSIONS AND DEATH. AUTOPSY: YELLOW SPINAL FLUID, EXTREME CONGESTION OF ALL OF THE VESSELS OF THE BRAIN, SCATTERED PETECHIAL HEMORRHAGES THROUGHOUT AND IN CHOROID PLEXUS AND ARACHNOID SPACE. ALSO HEMORRHAGE IN MYOCARDIUM, LUNGS, LIVER, KIDNEYS, ADRENALS AND PLEURÆ.

*Clinical History.* The patient, a male baby, one day old, was delivered by Cesarean section, spinal anesthesia having been used. During the course of the delivery the mother stopped breathing; artificial respiration was administered for two hours. At the end of this time the baby was delivered; he was blue and cyanotic with marked difficulty in breathing, and he had several convulsions. The following day he was brought to the Children's Hospital. Physical examination showed irregular and shallow respirations with periods of apnea. Coarse, crepitant râles were heard at the bases of both lungs. The skin was of a dusky color, indicating poor circulation. The baby was in the hospital for two hours before death. During this time there was one convulsion. Caffeine in small doses was given for the respiratory difficulty.

A lumbar puncture, performed postmortem, showed a yellow fluid with many red blood cells and few white blood cells.

*Summary of Autopsy. Cavities of the Body.* The peritoneal cavity shows no hemorrhages of the peritoneal surfaces. The visceral pleura and the visceral pericardium both show numerous hemorrhages, mostly along the course of the bloodvessels.

*Heart.* Gross examination shows numerous petechial hemorrhages into the myocardium and papillary muscles. Microscopic examination shows greatly congested bloodvessels and capillaries, especially marked in small areas of hemorrhage in the epicardium. Quite an extensive hemorrhage is found in the pericardium most marked about the larger branches of the coronary vessels.

*Lungs.* There is atelectasis. Congestion, with multiple hemorrhages extend well into the deep portions of the lung tissue. There is no gross picture of pneumonia, but the microscopic sections show acute bronchopneumonia.

*Spleen.* The only abnormality found is an extreme congestion.

*Gastrointestinal Tract.* There is no definite hemorrhage but considerable congestion in the mucosa and submucosa.

*Liver.* There is considerable hemorrhage into the liver substance. Microscopically there is seen some hematopoiesis; extreme congestion and a marked periportal infiltration of inflammatory cells.

*Kidney.* The pyramids are extremely congested. On microscopic examination, there are found to be multiple hemorrhages in the medulla with comparatively few such hemorrhages into the cortex.

*Adrenal.* The right adrenal shows a fairly large hemorrhage in the medulla. In the left adrenal there are several small hemorrhages chiefly in the medulla. The cortex is fairly normal.

*Gross Examination of the Brain.* The membranes—falx, tentorium and meninges—are intact and show no evidence of inflammatory reaction. There is a marked congestion of the vessels over the surface of the cortex and a few scattered, small areas of dark red, perivascular hemorrhage, measuring 0.5 to 1 cm. in diameter. There are a few small areas of sub-arachnoid hemorrhage over the frontal lobes. At the base of the brain there is similar congestion of the vessels; one small, dark-red hemorrhagic area appears at the cerebellopontine angle.

After hardening the brain in formalin for several weeks, it still is very soft and fluctuant with no ability to hold its shape. On making frontal sections, it is seen that the congestion, noticed upon the surface view, extends throughout the brain substance so that the injected bloodvessels stand out quite clearly. The choroid plexuses are congested. A section through the pons, peduncles and dentate nuclei, seem to show even more congestion, if possible, than the rest of the brain. A section through the medulla shows similar congestion.

*Microscopic Examination of the Brain.* Sections were made through several areas of the brain and cord, and were stained with hematoxylin and eosin, Morgan's hematoxylin<sup>4</sup> and cresyl violet.

A section through one of the subarachnoid hemorrhages of the frontal lobe shows sparse scatterings of red blood cells which have not as yet clotted, lying in the arachnoid space. Such hemorrhage is limited to rather a small area. In the brain substance below the surface there is marked congestion.

A section from the ventricular wall near the choroid plexus of the lateral ventricle shows extreme congestion of all the bloodvessels and capillaries. There are several small perivascular hemorrhages and in a few locations there are areas of more diffuse hemorrhage with a general scattering of red blood cells through the tissue.

A section through the corpus striatum on the left shows similar congestion and perivascular hemorrhage. There appears to be some edema; the perivascular and perineuronal spaces are swollen. The nerve cells of the basal ganglia are somewhat swollen and have undergone slight chromatolysis. The choroid plexus also shows extreme congestion. All the bloodvessels are packed with cells and there is extravasation of corpuscles into the interstitial spaces. This is of interest in relation to the yellow spinal fluid (Fig. 12).

A section passing through the hind brain and cerebellum, at the level of the pons and dentate nuclei, shows a degree of congestion even more marked than in those sections already described. Here all the bloodvessels and capillaries stand out as if an elaborate injection experiment had been performed. The richer blood supply of the gray matter shows in contrast to less vascular white matter. There is little hemorrhage at this level, but occasional perivascular hemorrhages may be found which are apt to occur around the larger vessels as well as around the capillaries (Fig. 13). The nerve cells are somewhat swollen and show chromatolysis.

A section through the upper spinal cord shows the same congestion, and here again the greater blood supply to the gray matter is apparent. There is slight edema, swelling of the nerve cells, and dilatation of the perivascular and perineuronal spaces. There is no hemorrhage seen in the cord.

Examination of sections stained with hematoxylin and eosin from various parts of the brain brings out the point that the veins are always much more congested than the arteries. This is especially apparent where, as in the meninges, a vein may be found lying near an artery. It is then observed that the artery although usually filled with blood is not at all distended whereas the vein usually is conspicuously distended. Numerous arteries were found which were almost empty with near-by veins extremely congested.

**Discussion.** The first case is one of hemorrhage associated with extensive sinus thrombosis. Here the thrombosis is most complete in the superior longitudinal sinus, extending into the lateral sinuses. Numerous cases of injuries resulting in thrombosis of the lateral sinuses have been reported, but interest in them seems to have been mainly from the point of view of otology. Injury to the superior longitudinal sinus is described much less frequently in the literature. In 1859 there was reported a case of traumatic obstruction of this sinus, the injury giving rise to no apparent continued intracranial disturbance.<sup>5</sup> This case was buried in the literature until the World War, when interest was aroused by the abundant cases of traumatic injury primary in the cerebral veins. In war wounds such injuries were quite common. Holmes and Sargent<sup>6</sup> present a review of 70 cases of war injuries involving the superior longitudinal sinus. The characteristic gross pathology which these cases showed was thrombosis of the superior longitudinal sinus with the cortical veins swollen, firm, and often thrombosed. The superior parts of the hemispheres drained by these veins were swollen and edematous, with the convolutions flattened out by pressure. Minute hemorrhages were present, and in a few cases, hemorrhagic softening with surrounding punctiform hemorrhages. The microscopic pathology of the affected areas showed edema and minute hemorrhages with many perivascular extravasations. If the lesions, as revealed by autopsy, are kept in mind, it is easy, as the authors point out, to understand the clinical symptoms. The motor symptoms were first those of the cortical areas nearest the median fissure and hence nearest the seat of the lesion, the superior longitudinal sinus.

Bagley<sup>7</sup> reviews 4 cases of extensive extravasation from the venous system of Galen. The clinical signs are: a sharp early rise in the temperature, pulse and respiration; a muscle disturbance chiefly of a spastic nature; blood in the spinal fluid; decreased intracranial pressure. Pathologically these cases show hemorrhagic extravasations varying in size from small microscopic lesions to large venous infarcts with extensive softening. Further light has recently been thrown on this subject by Doyle<sup>8</sup> who reports 4 cases of thrombosis of the superior longitudinal sinus.

Turning to the Case I reported here, one sees only slight similarity to the clinical features as reported by Holmes and Sargent and by Doyle. The pathologic picture bears a greater resemblance. The venous return of the blood is shut off as in the cases of sinus thrombosis reported by Holmes and Sargent and by Doyle; this is similar also to the cases of injury to the vein of Galen as reported by Bagley. Resulting from the venous stasis, there is a damming back of blood into the smaller vessels and a consequent hemorrhagic extravasation and softening. The probable cause of the softening and hemorrhage is discussed further in connection with the case of illuminating gas poisoning described below (Case IV).

The second case is quite similar to the first in several features. Here too there is sinus thrombosis, but this time following cerebral meningitis. The history presents a story of a discharging ear which is presumably the site from which the infection spread to the meninges of the brain, causing the meningitis, thrombosis of the pial veins with stasis of the deeper veins, anoxemia, softening and abscess formation. In this instance, the thrombosis is quite definitely the result of meningeal infection. The numerous punctate hemorrhages lead to a preliminary diagnosis of "hemorrhagic encephalitis." It would seem more logical to describe the hemorrhage and softening as direct results of the block in the venous return due to venous thrombosis.

The third case shows an extensive arachnoid hemorrhage. As is shown by the history, there is no trauma, no apparent cause for the condition. But a pericarditis was found at autopsy and thrombosis of the cerebral sinuses and veins. This arachnoid hemorrhage appears to have arisen from a venous disturbance. The clinical picture is analogous to that reported by Neal,<sup>12</sup> there was vomiting, fever and convulsions. The neck was not stiff, due, perhaps, to the fact that the hemorrhage was fairly well limited to the frontal and parietal lobes, leaving the base clear. As in the case reported by Neal, microscopic study shows pronounced edema, marked congestion of all the bloodvessels, particularly the capillaries, and numerous small petechial hemorrhages in the cortex. Of especial interest here, moreover, is the fact that the surface vessels are thrombosed which, along with the picture of edema and venous stasis, allows for an explanation of the hemorrhage on the same basis as in those cases already discussed: an occlusion of the venous return, a damming back of the venous blood and a consequent rupture of vessels, mostly in the brain substance, but of one at least in the subarachnoid space. It might be argued that the arachnoid hemorrhage occurred first and by pressure on the cortex obstructed the veins, thus causing cortical stasis. The pressure of extravasated thrombi were found in the pial veins. It seems more likely that the mechanism which caused the venous and capillary hemorrhages in the cortex, caused a vein in the arachnoid space to rupture.

In the past the discussion of subarachnoid hemorrhage<sup>9, 10, 11, 12</sup> centered almost entirely upon the arteries. No doubt many such hemorrhages are of arterial origin—certainly the most spectacular ones are. But is it not possible also to look for the etiology on the venous side?

The fourth case is rather an unusual case of poisoning from illuminating gas—unusual, not in the type of the lesion, but in its extent. The pathologic features of this type of cerebral injury are quite familiar. From a study of 63 cases of death from carbon monoxide poisoning, McNalley<sup>13</sup> describes a characteristic pathology: symmetrical punctate hemorrhage and softening in the globus pallidus, and less frequently similar lesions in the cortex. The microscopic pathology had been less often reported than the gross, but when described, it is the usual degenerative changes of nerve cells, demyelination, glial reactions, and the presence of gitter cells.<sup>14</sup> In addition, there is, in the cases of acute poisoning, hyperemia, so that all the vessels, not only the veins, but also the arteries and the smallest capillaries are congested and dilated.<sup>15</sup> Thus it is seen that the pathology, gross and microscopic, of the case reported here presents the usual features but with unusually extensive areas of hemorrhage and softening in the cortex.

Ruge<sup>16</sup> gives a review of the various explanations of softenings. These include the following viewpoints: that the lesion is the direct result of carbon monoxide on the bloodvessel walls resulting in fatty degeneration and rupture of the vessels; that the softenings result from thrombi; that the lesion is primary in the nervous tissue with a secondary vascular lesion. Ruge himself maintains that there is both a primary necrosis of the nerve cells and a vasomotor paralysis with subsequent stasis, which results in ischemia and nutritional disturbances. Ferraro and Morrison<sup>14</sup> found that in the acute stages of poisoning there was a swelling of the endothelium of the bloodvessels: they suggest that this swelling may reduce the lumen of the bloodvessel and so tend to cause nutritional changes of the nervous tissue. It is improbable that the lesion is primarily the effect of the gas poisoning upon the bloodvessels with hemorrhage and consequent softening, for similar lesions are found in Case V where asphyxia alone caused extreme congestion and numerous minute hemorrhages. Landis<sup>17</sup> had shown in his beautiful experiments that anoxemia causes increased permeability of the capillary walls. Anoxemia also causes degeneration of brain tissue, as in the ordinary arterial infarct. In the cases here presented the anoxemia comes from venous stasis and blood stagnation, not from ischemia, but the result on the brain tissue is the same: softening and hemorrhage. What causes the great dilatation of the veins in carbon monoxide poisoning is not known, but it has been observed in the pia to occur regularly and quickly after inhalation of CO<sub>1</sub>. Thus, although there is no gross block in the veins, as in the cases of

thrombosis described above, the slowed bloodflow and methemoglobinemia may cause enough anoxemia to make hemorrhages occur from the congested capillaries.

**Summary.** Five cases are presented which at autopsy showed hemorrhage into the parenchyma of the brain. In all of these the extravasation came from the veins and capillaries; there is no evidence that blood escaped from arteries. The mechanical factor common to all these cases is venous stasis, the common chemical factor is asphyxia. It is pointed out that widespread lesions can be caused by these two factors, the unit lesion being a petechial extravasation, but large lesions are formed by coalescence, and frank venous hemorrhage may be found. Such cases are more common than is generally supposed.

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## REVIEWS.

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MECHANO-THERAPY. By MARY REES MULLINER, M.D., Pp. 265; 57 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$2.75.

THE first part of this textbook deals with the procedures, the physiological effects and the technique of massage and movements. One chapter is devoted to the relation of the patient and operator and another one to planning the prescription of exercise for treatment. In the second part of the book the author discusses the treatment of various pathologic conditions by the means of massage and exercises.

The volume being on the whole well written, although rather elementary, should not be without value to nonmedical students and practitioners of mechanotherapy. J. N.

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FIBROADENOMATOSIS CYSTICA MAMMÆ AND ITS RELATION TO OTHER PATHOLOGICAL CONDITIONS IN THE MAMMA, ESPECIALLY CANCER. By CARL SEMB, formerly First Assistant in the Pathologico-anatomical Institute of the University Hospital, Oslo, Sweden. Pp. 484; 37 illustrations. Oslo: Nationaltykkeriet, 1928.

THE material studied was derived from 144 cases of fibroadenomatosis in women, and 14 in men, while for comparison the normal mammary glands from 32 cadavers were used.

The author concludes that the condition is neither an inflammation nor a tumor, but is a fibroepithelial proliferation that begins locally in the mammary tissue, and afterward extends diffusely over the whole mamma, with a tendency to bilateral occurrence. With the increasing development and irregularity there are formed multiple cysts, and in addition occasional independent multiple tumors such as papillomata of the milk ducts, fibroadenomata, cancer (and possibly, sarcoma). The disease can probably retrocede in the initial stages, but in its later stages it is hardly possible, especially when tumors are present.

In 52 per cent of the cases there was no histologic evidence or

suggestion of cancer; in 24 per cent there were appearances that might be interpreted as incipient cancer, and in 10 per cent histologic infiltrating cancer was present.

In 140 cases of carcinomatous breasts 60 per cent showed definite fibroadenomatosis of the noncancerous portions. Reasoning from the appearances found in his material, the author comes to the conclusion that "mammary cancer occurs up to 80 per cent as a secondary process in relation to fibroadenomatosis in one of its various forms."

He sees an analogy between what goes on in the mucous membranes of the mouth, throat, urogenital tract, and so forth, where there is a precancerous development of fibroepithelial papillomata, that afterward become cancerous and fibroepithelial growth with papillomata in the mamma. Fibroadenomatosis mammæ, therefore, must be conceived of as a precancerous condition, though all cases do not necessarily develop into cancer.

It is impossible to make an accurate differential diagnosis between "benign" and "malignant" cases, therefore the treatment is difficult. In young patients the excision of local areas may be sufficient, but in older ones, amputation of the breast may be better. It is inevitable that numerous breasts will be removed, in which no malignant change will be found, but such sacrifice is deemed justifiable.

J. McF.

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RECENT ADVANCES IN NEUROLOGY. By W. RUSSELL BRAIN, M.A., D.M., M.R.C.P., Assistant Physician to the London Hospital; Assistant Physician to the Hospital for Epilepsy and Paralysis, Maida Vale, and E. B. STRAUSS, B.A., M.B., B.CH., M.R.C.P., Medical Registrar to the Hospital for Epilepsy and Paralysis, Maida Vale; Clinical Assistant to the Medical Department, King's College Hospital. Pp. 412; 38 illustrations. Philadelphia: P. Blakiston's Son & Co., 1929. Price, \$3.50.

THE value of Pavlov's conditioned reflex is emphatically stated. From late studies of the tuber cinereum it is hinted, "the nervous system acts as an unsuspected integrator of many metabolic and endocrine functions." Various new "diseases" are considered. To mention some—dystrophia myotonica, erythroedema, epiloia and pyknolepsy. Refreshing optimism is shown in treatment and Roentgen rays are said to be helpful in new growths—even syringomyelia, neuralgias, inflammatory and infectious diseases of the central nervous system, certain "functional" nervous conditions and some traumatic lesions. The twelve appended cerebrospinal fluid "pictures" are helpful.

This excellent book is destined to fulfill the needs of those seeking recent advances in neurology.

N. Y.

THROMBOANGIITIS OBLITERANS—CLINICAL, PHYSIOLOGIC AND PATHOLOGIC STUDIES. By GEORGE E. BROWN, M.D., and EDGAR V. ALLEN, M.D., Division of Medicine, Mayo Clinic, Collaborating in PATHOLOGY with HOWARD R. MAHORNER, M.D., Fellow in Surgery, The Mayo Foundation. Pp. 219; 62 illustrations. Philadelphia and London: W. B. Saunders Company, 1928. Price, \$3.00.

AN excellent presentation of the clinical and pathologic picture of thromboangiitis obliterans, the problems of diagnosis, and the indications for, and methods of treatment: based on an experience of over 300 cases seen in the Mayo Clinic and on a thorough survey of the literature. It is significant that in this malady a satisfactory result may often be obtained by treatment measures other than amputation, provided that the diagnosis be made sufficiently early. The reader will, therefore, find especially useful the discussion of the differential diagnosis of this condition from other forms of arterial disease, notably Raynaud's disease, erythromelalgia and arteriosclerosis.

R. K.

THE BIOCHEMISTRY OF THE AMINO ACIDS. BY H. H. MITCHELL and T. S. HAMILTON. The University of Illinois. Pp. 619; 21 illustrations. American Chemical Society Monograph Series. No. 48. New York City: The Chemical Catalog Company, Inc., 1929. Price, \$9.50.

THIS book is a much needed review of the present status of research on the rôle of amino acids in animal metabolism. Of the ten chapters in the book all are devoted to various phases of amino-acid metabolism except the first three which cover physical and chemical properties of amino acids and methods for their determination, both separately and in hydrolytic mixtures. The opening chapter on physical and chemical properties is unfortunately somewhat marred by lack of completeness and occasional inaccuracies.

The authors, as indicated in their preface, make a definite attempt to present a survey of past research in the field of amino-acid metabolism with especial emphasis on the critical weighing of divergent conclusions of different investigators, and to pass judgment in such cases as to their relative values. Perhaps one of the most valuable features of the book is its insistence on the quantitative side of nutritional studies. The authors set up a rigorous standard for the quality of proof required for definite conclusions. These requirements, if taken seriously by nutritional workers should do much to bring order out of the comparative confusion now existing.

J. A.

INJECTION TREATMENT OF INTERNAL HEMORRHOIDS. By MARION C. PRUITT, M.D., L.R.C.P., S. (Ed.), F.R.C.S. (Ed.), F.A.C.S. Pp. 137; 9 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$3.00.

THIS little book gives an admirable presentation of the subject of hemorrhoids. Several chapters are given over to the anatomy, etiology, pathology and symptomatology as well as treatment. Unbiased quotations from recognized authorities are frequently used for and against both surgical and injection treatment.

The injection treatment is described in detail and advanced for almost general use. The author acknowledges that recurrence after injection is probably more frequent than after surgery, but he argues that the injected patient will return for a second treatment whereas the patient treated by operative surgery is frequently deterred because of his previous painful experience.

The work is interesting and instructive.

E. E.

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THE CLIMACTERIC. (THE CRITICAL AGE.) By GREGORIO MARANON, Professor of Medical Pathology in the Madrid General Hospital. Translated by K. S. STEVENS. Edited by CAREY CULBERTSON, A.B., M.D., F.A.C.S., Associate Clinical Professor of Obstetrics and Gynecology, Rush Medical College. First American edition from second Spanish edition. Pp. 425; 18 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$6.50.

A PERUSAL of this book quickly demonstrates that it is concerned with a much broader subject than the mere cessation of the menses. The author differentiates clearly between the menopause, which is merely a simple genital incident in woman and the climacteric, occupying a long period of life, the nucleus of which is the genital subsidence, but in the development of which all organic activities participate. An interesting section is devoted to the critical age in the male. The scattered editorial comments of Culbertson are quite acceptable to readers of this American edition. The work is encyclopedic in character, presents some interesting theories and can be recommended as a reference book.

F. B.

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YOU AND THE DOCTOR. By JOHN B. HAWES, 2d, M.D. Pp. 181. Boston and New York: Houghton Mifflin Company, 1929. Price, \$2.00.

It is perhaps fortunate for the conscientious members of the medical profession that they are not apt to be aware of the degree to

which their aims and aspirations are misunderstood by the general public. Granted the truth of such an unwelcome state of affairs, the benefit of such a book as the one under review to the medical profession, as well as to the public is obvious. And if the type of book is desirable, it is doubly so when written by such a sound conservative authority as Dr. Hawes, who, as the blurb tells us, is "a famous doctor . . . of great reputation." To make assurance doubly sure the book has been censored by six friendly experts and launched with an approving introduction by Dr. R. C. Cabot. While it will probably most frequently be found where it is least needed—in the doctor's waiting room—it is to be hoped that it may be possible to circulate it among those who wait too long for medical aid. "Call the doctor at once" is the chief refrain and properly so for the conditions discussed. Perusal of the greater part of the book offers much sane advice to commend, nothing to object to, and but few important omissions—a hypercriticism at best in such a work.

E. K.

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A MANUAL OF EXTERNAL PARASITES. By HENRY ELLSWORTH EWING, PH.D., United States Bureau of Entomology, Washington, D. C. Pp. 225; 96 illustrations. Springfield, Ill.: Charles C. Thomas, 1929. Price, \$4.50.

A TAXONOMIC summary of the five major groups of ectoparasitic arthropods: The mites, ticks, biting lice, sucking lice and fleas. Keys are given, in most instances, to the known genera of the world, and are supplemented by figures of important species. Descriptions of new genera, proposed in the text and included in the keys, are given in an appendix. The author has also included short discussions of life histories, natural relationships, geographical distribution, parasitic habits and economic importance of the various groups, and has added practical suggestions for control.

H. R.

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THE CLINICAL ASPECTS OF VENOUS PRESSURE. By J. A. E. EYSTER, B.Sc., M.D., Professor of Physiology, University of Wisconsin and Associate Physician, Wisconsin General Hospital. Pp. 135; 7 illustrations. New York: Macmillan Company, 1929. Price, \$2.50.

THOUGH adequate indirect methods for measuring the venous blood pressure have now existed for over twenty years, this clinical test has received but little attention in this country, except from the Wisconsin group of which the author is a prominent member. And yet it has been repeatedly demonstrated that it is a valuable clinical

method; often, for instance, demonstrating an approaching cardiac failure before any other signs are positive. The present booklet, then, small, inexpensive, easily comprehended and written by an acknowledged authority on the subject, is a welcome and valuable addition to our medical literature and one that merits a wide distribution. When one considers the importance of chronic passive congestion of the viscera in heart disease, both in its direct effect on the condition of the patient as well as an indication of the cardiac efficiency at the moment, it is not too much to say that venous pressure should be followed in cardiac cases as routinely as is the arterial pressure today. Eyster's book will tell you how easily it can be estimated and the significance of the results found. Such typographical errors as "parthenthesis" (p. vii), "Reynaud" (p. 13), "Haidenheim" (p. 15), "Samana" (p. 134) indicate a certain amount of regrettable carelessness in the proof reading that was fortunately not present in the writing.

E. K.

## BOOKS RECEIVED.

### NEW BOOKS.

*The Principles of Clinical Pathology in Practice.\** By GEOFFREY BOURNE, M.D. (LOND.), M.R.C.P. and KENNETH STONE, M.D. (OXON.), M.R.C.P. Pp. 392; 10 illustrations. New York: Oxford University Press, American Branch, 1929.

*Surgical and Medical Gynecologic Technic.\** By THOMAS H. CHERRY, M.D., F.A.C.S. Pp. 678; 558 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$8.00.

*Minor Surgery.\** By FREDERICK B. CHRISTOPHER, M.D. Pp. 694; 465 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$8.00.

*Some Principles of Minor Surgery.\** By ZACHARY COPE, M.S., M.D. (LOND.), F.R.C.S. (ENG.). Pp. 159; 82 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$3.50.

*Endocrine Disorders.\** By PROF. HANS CURSCHMANN. Pp. 188; 46 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$4.00.

*Sterilization for Human Betterment.\** By E. S. GOSNEY, B.S., LL.B. and PAUL POPENOE, D.Sc. Pp. 202. New York: The Macmillan Company, 1929. Price, \$2.00.

*An Introduction to Pharmacology and Therapeutics.\** By J. A. GUNN, M.D., D.Sc. (EDIN.), M.A. (OXON.). Pp. 220. New York: Oxford University Press, American Branch, 1929.

\* Reviews of titles followed by an asterisk will appear in a later number.

- Rickets Including Osteomalacia and Tetany.\** By ALFRED F. HESS, M.D. Pp. 485; 52 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$5.50.
- Tuberculous Intoxications.\** By JOSEPH HOLLÉS, M.D. Pp. 132. New York: William Wood & Co., 1929. Price, \$3.25.
- James Mackenzie Institute for Clinical Research. Gastro-Intestinal Diseases.\** Edited by PROF. DAVID WATERSTON, M.A., M.D., F.R.C.S. (EDIN.). Pp. 278; 13 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$3.25.
- Varicose Veins.\** By H. O. MCPHEETERS, M.D., F.A.C.S. Pp. 208; 34 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$3.50.
- Abstracts, Proceedings of Meetings of New York Pathological Society, 1927-1928.* Pp. 71.
- Dedication of the Montgomery Ward Memorial Building Northwestern University Medical School.* Pp. 193; illustrated. Chicago: Northwestern University Press, 1929.
- Combined Sinus and Duodenal Infections.* By S. PESKIND, B.S., M.D. Pp. 20. Privately printed, S. Peskind, Cleveland, Ohio.
- Outline of Preventive Medicine.\** Twenty-one contributors. Pp. 398. New York: Paul B. Hoeber, Inc., 1929. Price, \$5.00.
- Practical Handbook for Diabetic Patients.\** By ABRAHAM RUDY, M.D. Pp. 180; 7 illustrations. Boston: M. Barrows & Co., 1929. Price, \$2.00.
- United Fruit Company Medical Department, Seventeenth Annual Report, 1928.* Pp. 381; illustrated. Boston: United Fruit Company, 1929.
- The Common Head Cold and Its Complications.\** By WALTER A. WELLS, A.M., M.D., F.A.C.S. Pp. 225; 15 illustrations. New York: The Macmillan Company, 1929. Price, \$2.75.

### NEW EDITIONS.

- Medical State Board Questions and Answers.* By R. MAX GOEPP, M.D. Pp. 754. Sixth edition. Philadelphia: W. B. Saunders Company, 1929. Price, \$6.00.
- A Study of Masturbation and The Psychosexual Life.* By JOHN F. W. MEAGHER, M.D., F.A.C.P. Second edition. Pp. 130. New York: William Wood & Co., 1929. Price, \$2.00.
- Diseases of the Chest.* By GEORGE WILLIAM NORRIS, A.B., M.D. and HENRY R. M. LANDIS, A.B., M.D., Sc.D. Pp. 954; 478 illustrations. Fourth edition. Philadelphia: W. B. Saunders Company.
- A first class book welcome in each new edition. In this fourth edition a chapter on the transmission of sounds through the chest by C. M. Montgomery has been added; also a brief account of bronchoscopic diagnosis by L. H. Clerf.
- Pathogenic Microorganisms.* By WILLIAM H. PARK, M.D., ANNA WESSELS WILLIAMS, M.D. and CHARLES KRUMWIEDE, M.D. Ninth edition. Pp. 819; 225 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$6.50.
- A deservedly well-known book. The chief developments of the past three years have been included (scarlet fever, measles, yellow and undulant fevers, tularemia, new types of pneumococci, etc.).

\* Reviews of titles followed by an asterisk will appear in a later number.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

W. S. THAYER, M.D.,

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AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

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**The Arterioles in Cases of Hypertension.**—Biopsy is becoming more and more to be utilized not only by the surgeons but by clinicians as well in various types of studies of living tissue. One of the most interesting results from the examination of biopsy material is presented in an article by KERNOHAN, ANDERSON and KEITH (*Arch. Int. Med.*, 1929, 44, 395). These investigators studied the arterioles of muscle tissue removed from the pectoralis major of patients suffering from hypertension. Muscle tissue was utilized because it makes up over one-third of the body mass and it seems fair to assume that if the arterioles are involved by pathologic changes it certainly would be possible to demonstrate such alterations from the normal in the bloodvessels of muscle. After a thorough review of the pertinent literature relative to the study of the small bloodvessels, the results of the findings are recorded in the three types of hypertension in which the arteriolar condition was investigated: (1) Benign hypertension; (2) an intermittent group presenting the syndrome of severe benign or early malignant hypertension; (3) malignant hypertension. From the point of view of the clinical manifestations of the condition, it might be said that the maximal blood pressure in benign cases was 240 systolic and 145 diastolic. In the intermittent group it was 280 systolic and 160 diastolic; in the malignant type it was 320 systolic and 180 diastolic. Cardiac hypertrophy, peripheral sclerosis, retinal sclerosis, albuminuria, evidences of renal insufficiency and anemia were also noted; all these customary findings naturally being much less pronounced in the benign cases than in the other two groups of cases. The authors worked out a scheme for determining the relation of the vessel wall to the lumen of the arteriole. Normally this ratio is as 1 to 2. In the cases of benign hypertension the average ratio was 1 to 1.4 with a variation of from



1 to 1.4 to 1 to 1.8. The intermittent and the malignant hypertension ratio for the wall of the lumen was practically the same. The authors do not believe that it is possible to distinguish the special types of hypertension from histologic study of fresh tissue. The study indicates definitely that there is associated with hypertension a diffuse disturbance of the arterial vascular system. In the great majority of cases the malignant syndrome does not develop. The authors state that any possible theory as to the cause of diffuse vascular hypertensive disease must explain the slow progress in benign hypertension, the rapid development of the course of malignant hypertension, and the gradual transition from benign to malignant hypertension in some cases of chronic nephritis. They suggest two general possibilities as the cause of the condition: (1) An inherent disturbance in the nervous system, or (2) the action of an hypothetic pressor substance on the sympathetic chain, on sympathetic endings in the wall of the arteriole or directly on the smooth muscle of the wall.

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**The Incidence of Infection with *Endamoeba Histolytica* in Louisiana as Determined by Comparative Microscopic and Cultural Methods.**—JOHNS and TRIFOLI (*New Orleans Med. and Surg. J.*, 1929, 82, 224) write that the incidence of infection with *Endamoeba histolytica* necessarily would represent not only those who are suffering from the active manifestations of amebiasis, but also a still larger number of individuals who are carriers of the infective cysts. On account of the difficulty of making large series of examinations, it has been impossible to make surveys of the general population for carrier incidence as well as for the frequency of amoebas. This is really a problem of importance, bearing in mind that the disease has not decreased as have other enteric diseases with the institution of modern sanitary handling of water and milk. Also, it should be remembered that the carrier is producing and discharging an enormous number of parasitic cysts and that potentially he is not only likely to develop active symptoms, but also liver abscess may develop in an individual who is a carrier without the occurrence of symptoms of active dysentery. The authors' study represents a series of 554 examinations, the stools being examined both directly following passage by the centrifuge-concentration method and by the utilization of a special method of culturing the feces. In the majority of cases only one specimen was examined, but it is believed that the great majority of infections may be demonstrated from the preliminary or original examination. Incidentally, it has been found that the direct examination of the stools and culturing the stools give figures which are approximately identical. It was found that 36, or 7.44 per cent, of the individuals were infested with *Endamoeba histolytica*. Dividing these individuals into groups, it was found that in private patients to the number of 130, 6.92 per cent were infected. Of 180 medical students, 8.33 per cent and of 234 patients in Charity Hospital 7.22 per cent were infected. In only 1 per cent of the infected individuals were there any definite symptoms of dysentery or were the vegetative forms of the parasite present. Considering the three sources from which the specimens were obtained, the authors felt that 7.44 per cent represents a fair index of the infection in this particular state in the South.

## SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

**Cholecystography.**—ROBINS (*New England J. Med.*, 1929, 201, 114) states that the sudden impetus in the advancement of knowledge regarding gall-bladder physiology must be attributed to cholecystography. The emptying and concentrating function of the gall bladder was little understood. Graham believes that the gall bladder is emptied by the elastic recoil of the distended viscus on release of the common duct sphincter, the inflow and outflow of bile from the liver through the periodic closing and opening of the sphincter, and suction due to the stream of bile from the liver as it passes the mouth of the cystic duct. The basis of his arguments is that the gall bladder has never been seen to contract spontaneously. Experimental evidence lends very little support to the effect of respiration. Another important function is the concentration of bile. This is the fundamental reason why cholecystography is feasible. Rous and McMaster showed that the gall bladder could concentrate the bile seven times or more in twenty-four hours, the process being accomplished by osmosis and diffusion. The technique of cholecystography must be exact. Care must be taken that the patient holds his breath during the exposure of film. The slightest motion may lead to erroneous conclusions. The normal gall bladder is densely outlined and is oblong or pear shaped. It should empty completely or contract to about one-third of its original size two hours after a fat-protein meal. Pathologically, gall bladders may be divided into three groups: Disease of the mucous membrane; disease of the muscle and change of the serosa. He takes up the reasons for failure to visualize the gall-bladder shadow.

**Variations in the Extra Hepatic Biliary Tract.**—BEAVER (*Arch. Surg.*, 1929, 19, 321) says that the normal angular mode of juncture of the cystic duct with the hepatic duct, as described in textbooks of anatomy occurred in only a little more than half of the cases. The long and short parallel types of cystic duct occur in more than a third of the cases and, as is shown by the literature, is perhaps the most common cause of accidents in biliary surgery. In such cases there is a marked increase in the length of the cystic duct and a corresponding decrease in that of the common bile duct. The cystic duct and the hepatic duct are so intimately bound together by fibrous tissue that they are absolutely inseparable and thus appear as a single duct. Any rough manipulation may tear the thin septum which exists between them. The large portion of a cystic duct of this type which remains following cholecystectomy may dilate and form a new gall bladder, probably with recurrence of symptoms. The cystic duct does not contain valves of Heister in the portion which lies parallel to the hepatic duct. It has been recorded

that strong traction on the gall bladder is much more likely to tear off a spiral cystic duct than a duct with a normal arrangement. Accessory hepatic ducts occurred in 5 cases or 8.7 per cent of this series. Four of these were accessory right hepatic ducts 3 of which were also accessory to the cystic duct. The length and diameter of the accessory ducts corresponded closely to the normal cystic duct.

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**Hyperglycemia Following Head Injuries.**—MOCK and DE TAKATS (*Ann. Surg.*, 1929, 90, 190) state that head injuries of sufficient severity to cause loss of consciousness result constantly in hyperglycemia, which subsides within the first day or a few days. This has been found in animal experiments and in a small number of clinical cases. Section of the splanchnic nerves in the dog abolished this hyperglycemia. The sympathetic discharge originating in the higher centers of sugar regulation is unable to reach the liver and mobilize glycogen. This state of sympatheticonia manifesting itself in increased epinephrin susceptibility was tested in patients shortly after and many months after head injury. While the immediate response was stronger than in controls, the late curves were mostly negative with the exception of those who had marked residual damage. A few patients were found whose epinephrin curve was not abnormally high, but showed a delay in returning to normal. These patients were all above forty years of age and may have mild pancreatic damage. This is not uncommon at this age and deserves careful consideration. Theoretically the possibility of upsetting an already weakened pancreatic activity by a sudden sympathetic discharge, followed by a marked rise in blood sugar must be considered.

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**Acute Fractures of the Shaft of the Femur in Children.**—CONWELL (*J. Bone and Joint Surg.*, 1929, 11, 593) declares that there is unlimited literature on fractures of the femur in children. Plaster cast, plaster cast and extension, and suspension and extension, are the main forms of treatment. Excellent results are obtained by various surgeons by all of the above methods. The suspension and extension method is the most popular. Treatment by open reduction should be the last resort and usually is not necessary. A summary of the results of the cases treated by plaster cast shows that better results are obtained in the very young than in the older child. A summary of the cases treated in plaster cast and extension shows that better results are obtained in the older child. Careful physical and radiologic examinations with careful history of the accident should always be made. Immediate reduction with aid of fluoroscope should be done. Every case of fractured femur should be considered an emergency and immediate treatment should be given following injury. Good alignment is most important, then bone approximation. It is definitely concluded that compensatory lengthening does take place, also correction of poor alignment, but chiefly in patients before the age of eight years. The suspension and extension method is by far the most comfortable dressing, and best results have been obtained by this method. Granting that compensatory lengthening does take place and that serious misalignments are corrected in fractures of the femur in children, no surgeon is justified in neglecting anyone of the important things which should be done immediately following a fracture of the femur.

## THERAPEUTICS

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UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,  
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,  
BOSTON, MASS.

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**Treatment of Hay Fever.**—According to VON LEEUWEN (*Therap. d. Gegen.*, 1929, 70, 244), patients who show manifestations of hay fever throughout the year (rhinitis vasomotoria) should be separated from the ones with true hay fever caused by pollens. The sensitivity of the skin and mucous membranes to pollens is parallel. The author prefers the cutaneous test to the intracutaneous one as the latter may induce marked systemic reactions. The cutaneous test is performed by inducing a small scarification of the skin and rubbing in 1 to 2 drops of pollen extract. With a positive reaction a wheal with a surrounding flare develops within five to ten minutes. For general practice it is sufficient to use two mixtures of extracts. One of the extracts is a mixture of a number of grains and the other is a mixture of various weeds. In the treatment of hay fever the most important measure is the preventive one. The patient should avoid exposure to pollens as much as possible. Complete desensitization cannot be achieved; one can expect but a reduction in sensitivity. In the desensitization, specific and nonspecific agents are applied. Among the nonspecific agents the author prefers the tuberculin therapy. Patients with allergy show a strongly positive von Pirquet reaction. The injection of tuberculin has a beneficial influence on both asthma and hay fever. The treatment for hay fever starts usually in March or April; the initial dose is 0.1 cc. of a dilution of 1 to 100,000. The injection is repeated three times weekly; the dosage increased by 0.1 cc. with each injection. When a total dose of 1 cc. is reached the injections are continued with a dose of 0.1 cc. of a dilution of 1 to 10,000. With the onset of strong local or general reaction the treatment is discontinued for a week, after which it is resumed again, starting with a smaller dose and gradually raising the amount injected. With the onset of the hay fever season only one injection is given a week and the dosage is not raised. After the season is over the injections are discontinued until they are resumed in the next season. Tuberculin therapy alone is insufficient to induce marked reduction in sensitivity in the majority of cases, and additionally specific therapy is used, according to whether the patient is sensitive to grain mixtures or weed mixtures. A solution containing a mixture of grains or weeds is injected with an initial dose of 0.5 cc. of 1 to 1,000,000. The injections are continued with gradually increasing doses three times a week. If mild reaction (conjunctivitis or rhinitis)

develops the treatment is discontinued for two or three days, then it is renewed in smaller amounts and the dosage is raised cautiously. Development of neuritis contraindicates the treatment instantly. With the onset of the hay fever season, the amount injected should not be further raised. Individual sensitivity may alter the amounts to be administered considerably. Even after successful desensitization the positive skin reaction persists, though with less intensity. Among the therapeutic measures which are useful in the treatment of hay fever, following its clinical manifestation, are adrenalin, ephedrin and aspirin. The application of paraffin in form of salves over the mucous membrane and the protection of the eyes against light by wearing dark glasses may also be beneficial. The intravenous administration of calcium chloride is also advocated.

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**The Treatment of Exophthalmic Goiter.**—The spontaneous recoveries of patients with exophthalmic goiter make the evaluation of therapeutic measures difficult. A critical study is presented by DON (*Brit. Med. J.*, 1929, i, 1108) on the relative value of: (1) rest combined with iodine; (2) Roentgen ray therapy; (3) operative procedure.

The effects of iodine were observed in 36 cases in which the rate of the basal metabolism varied between +30 and +114 per cent. Lugol's solution was given in doses of 20 to 30 minims a day. Definite temporary improvement followed this treatment in 84 per cent of the cases. In 16 cases the effect of a second course of treatment was studied. In only 37 per cent of the cases was a second course equal to the first in effectiveness. The maximal fall in the basal metabolism and the pulse rate was reached in ten to fourteen days. Iodine itself cannot cure exophthalmic goiter, and therefore it should be held back until operation is decided upon. Iodine is an excellent therapeutic agent for thyroid crisis with vomiting, but if a course has already been given, its value may be disappointing. During the iodine administration the patients often gain weight.

There is still considerable skepticism concerning the value of Roentgen ray therapy. The effect of Roentgen ray therapy was investigated in 23 patients with exophthalmic goiter and with a basal metabolism more than +30 per cent. Treatments were given at first twice a week, then once a week, and the intervals were gradually lengthened until a total of about 30 doses (one dose equal to a quarter of an erythema dose) were administered over a year. In 12 of the cases there was either a cure or marked improvement. This improvement was obvious in most cases by the third month, and in all cases by the sixth month. If no signs of improvement are present at the end of the sixth month, it is doubtful if further Roentgen ray therapy will be of benefit. Cases with short history of the disease and small goiter had the best tendency to benefit by Roentgen ray treatment.

The merit of the operative treatment was tested on 25 patients, after preparation with Lugol's iodine, 10 minims three times a day. Operation was performed only if the basal metabolism was under +30 per cent. Thyroidectomy was performed on 21 patients. Eighty per cent of the patients operated on became cured, or considerably benefited for at least one year after operation. It cannot be too strongly emphasized that surgical intervention should only be undertaken by an

experienced surgeon. Operative treatment is the most effective therapy for exophthalmic goiter.

Don concludes that the patient should be given six months' trial with Roentgen ray therapy; then, if improvement does not occur, the patient should be sent to an experienced surgeon for operation if the case is suitable.

## PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

**Successive Roentgenograms of the Chest of Children During Measles.**  
—KOHN and KIORENSKY (*Am. J. Dis. Child.*, 1929, 38, 258) had successive roentgenograms of the chest taken in 30 children between the ages of seven months and twelve years in the various stages of measles. Infiltrations of the lung was seen for the first time in the pictures in the præruptive, eruptive and posteruptive stages. These were present in 62.4 per cent of the patients less than four years of age and in 42.2 per cent of the patients four years or over. In those cases showing pulmonary infiltration, this was present in 61 per cent of the cases before or during the height of the eruption. The infiltrations were of three types; large, homogenous triangles; large homogenous opacities obscuring the hilum and the paravertebral regions; and disseminated, confluent, fine and coarse mottling in various areas of the lung field. For the latter type a common site was in the cardiophrenic angles. The most infrequent site was the right lower lobe; the right upper, the left lower, the right upper and right middle lobes following in the order given. The infiltrations were most dense during the receding eruptive or posteruptive stage. In 27 cases shadows suggesting infiltration of the lung appeared and continued to progress after the temperature of the child was normal. In these cases there were no definite physical signs. In the group in which no pulmonary infiltration was seen 79.2 per cent of the patients gave clinically mild courses of measles while in those cases in which pulmonary infiltrations appeared in the pictures 44.4 per cent were mild. Physical signs of bronchial or pulmonary involvement were present in 14 per cent of those which showed no pulmonary infiltration on the roentgenogram and in 47 per cent of those which did show pulmonary infiltration. It was impossible to predict from the physical examination during the eruptive stage which cases would show pulmonary infiltration in the roentgenogram. Abnormal intensity of the pulmonary markings was present in 80 per cent of all cases. Their appearance in the plates in children four years and over was somewhat different from those in children less than four years.

**The Effect on Digestion and Assimilation of Including Bananas in Mixed Diet of Children Over Five Years of Age.**—BROWN and COURTNEY (*Can. Med. Assn. J.* 1929, 21, 37) studied children between the

ages of five and thirteen years of age in groups of 4, having 2 on a mixed diet without bananas and 2 on the same diet with from three to six bananas substituted for an equivalent amount of carbohydrate. After a suitable interval the diet of the two pairs were transposed. A preliminary period on a measured food intake was followed by the taking of representative samples of the diet and the fecal and urinary output of each child were collected over a four-day period. This material was analyzed for the content of fat, nitrogen, total ash, calcium, magnesium, phosphorus and chlorid. The moist and dried weight of the feces and the volume of urine were noted daily and the hydrogen-ion concentration was estimated in the fresh urine and feces. The percentage of intake retained was taken as the standard of digestion and assimilation. In respect to nitrogen retention the difference was somewhat greater than for the other components determined, but it is questionable whether this difference is sufficient to be of any significance. The averages for the group periods showed small differences, sometime to the advantage to the banana-containing diet and sometime to that of the control diet. There was always a somewhat greater output of feces during the banana feeding than during the controlled diet, but there never was any diarrhea on the banana diet. The urine was always distinctly more alkaline with the banana-containing diet than with the control diet as shown by the hydrogen-ion values. This suggests, that the banana may be of value for addition to diets in acid conditions.

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**The Status of the Therapeutics of Irradiated Ergosterol.**—HESS, LEWIS and RIVKIN (*J. Am. Med. Assn.*, 1929, 93, 661) after further clinical experiments state that preparations of irradiated ergosterol is specific for rickets, tetany and osteomalatia. It has not been proved of definite value in other clinical conditions. During the past year the dosage has been established for the prevention and cure of rickets. Premature and exceptionally rapid growing infants may be regarded as a separate group and the dosage gauged according to a different scale. The basis of this standardization is a biologic estimation of the antirachitic potency rather than a gravimetric assay of the irradiated ergosterol. It was found that if the prescribed dosage is observed toxic symptoms and hypercalcemia need not be feared. These phenomena seem to be entirely or almost entirely due to an excess of antirachitic action. Hypercalcemia also can be produced experimentally by giving undue amounts of cod-liver oil. Irradiated milk, especially dried milk is also a valuable product in combating rickets and tetany and most especially in their prevention. It is not believed that irradiated cereals will play any rôle in the control of rickets because of the numerous technical difficulties involved in the course of activation, such biologic products as irradiated ergosterol and irradiated foods should be subject to careful laboratory control.

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**The Intermuscular Injection of Adult Whole Blood as Prophylaxis Against Measles.**—BADER (*J. Am. Med. Assn.*, 1929, 93, 668) used from 20 to 30 cc. of the whole blood of persons recovered from measles in 30 patients from six months to forty-two months of age. The donors had recovered from measles from two to twenty-five years before the

treatment. This blood which was given within the first seven days following exposure completely protected 12 patients insofar as the escape from measles is a proof of protection. It was followed in 9 cases by a modified and attenuated type of measles without catarrhal symptoms. In 8 patients mild catarrhal symptoms were present. One child had measles of moderate severity and she was the only one of the 30 cases which showed Koplik spots and a typical eruption. In the others in whom there were eruptions these were not characteristic. In all but 2 cases there was distinct modification of temperature. In all except possibly 4 cases there was an apparent prolongation of the period of incubation. No complications developed. From this study it would seem that whole blood from adults even long recovered from measles is an effective measure against measles. It is suggested that it might be completely efficacious for institutions where many cross infections are found when the serum from recently convalescent patients is not readily available, or in the age group under five years in which 90 per cent of the deaths from measles occur, or in the weak and debilitated where measles might end fatally.

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**The Leukocyte Picture in Measles.**—OLECHNOWIEZ (*Rev. Franc. de. Ped.*, 1929, 5, 209) made 274 examinations of the blood in 32 infants and children ill with measles. He found that the leukocyte picture was a valuable aid in the diagnosis and prognosis. He found that the kind and number of leukocytes in measles vary. In the incubation period hyperleukocytosis and slight displacement of the neutrophils to the left are present and eosinophilia is common. In the period of invasion there are leukopenia and displacement of the neutrophils to the left in the benign cases in which the prognosis is given, and hyperleukocytosis, hyperlymphocytosis and a decreased number or absence of monocytes and eosinophils in the severe cases in which the prognosis is bad. In the post eruptive period there are slight leukocytosis, slight lymphocytosis or normal lymphocythemia and an increased number of eosinophils and monocytes. In measles in children of less than four years of age the leukocyte picture is variable.

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**The Immunologic Researches on Whooping Cough.**—DEBRÉ, MARIE and PRÉTET (*Ann. de. med.*, 1929, 25, 434) studied colonies of *Pertussis bacilli* obtained by cultivating droplets from patients with whooping cough. In this manner they isolated and cultivated a large number of strains of *Pertussis bacilli*. They attempted to determine whether or not these strains belonged to the same type and they found that none of the bacilli was agglutinated by experimental serum A, while bacilli of the control culture were agglutinated by this serum in concentration of 1 to 1000. The bacilli of all of the strains were agglutinated with serum B, most of them at a concentration of 1 to 1500 or 1 to 1000. The bacilli of the control culture did not show agglutination to this serum. The bacilli of only 5 of the cultures were agglutinated by therapeutic serum of Bordet-Gengou. The agglutinating serums agglutinated bacilli of all the strains at concentrations varying of from 1 to 500 to 1 to 4000. Only bacilli of the control culture were not agglutinated. This study showed that the strains of bacilli studied were of a homogeneous nature.



## DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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**The Nonvenereal Affections of the Genitalia.**—SEMON (*Brit. J. Ven. Dis.*, 1929, 5, 144) discusses conditions of the genitalia commonly seen by the dermatologist. Chief among local expressions is the occurrence of eczema usually as moist intertrigo. Occasionally eczema is associated with thread-worms, rectal fissures or an underlying mycosis. A chronic dry pruritic form is of neurogenic significance. Psoriasis may appear on the genitalia as its sole localization, and as such is important in differential diagnosis from the nonulcerative late syphilide. Lichen planus of the penis is usually nonpruritic and may persist for months or years. Urticaria in the form of Quincke's edema is prone to attack the scrotum or a single labium majus. It is painless, afebrile and unaccompanied by glandular swelling, all of which should protect the patient from surgical intervention. Its sudden onset and history of previous attacks is likewise characteristic. The author has used intravenous injections of afenil (calcium-urea compound with good success. Medicinal eruptions include the genital reactions to antipyrine and phenolphthalein and the lesions of dermatitis venenata resulting from petroleum products, quinin in pessaries and certain mercurial ointments. Erythema multiforme and pemphigus frequently present their primary signs on the genitalia in the form of bullæ and often ulcers. Anogenital pruritus includes patients in two main categories, the well-nourished, opulent middle-aged man of sedentary habits and the nervous high-strung woman of temperate and otherwise blameless disposition. Frequently fungi can be demonstrated in this type of case, and in a high proportion relief is obtained by the empirical use of fungicidal ointments. Pediculi and scabies are important, quite as much as a result of improper measures sometimes employed in their treatment as because of the disease itself. Herpes genitalis and condyloma acuminatum appear to be conveyed by sexual intercourse and are often confused with more serious conditions. Molluscum contagiosum may assume the gigantic type, occasionally is subject to secondary infection and frequently remains unchanged for years. Important among the nonvenereal ulcers are those due to mechanical, chemical or thermal trauma; the acute tuberculous ulcer, the diphtheritic ulcer and the gangrenous ulcer of varied etiology.

Dr. T. Anwyl Davies, in discussing the author's paper, emphasized the *Trichomonas vaginalis* as a not uncommon cause of vaginitis. This parasite appears to become pathogenic in the presence of other organisms favoring its growth. Dark-field examination is the best method to demonstrate its presence in the secretion. The patients

complain of a severe irritation and a greenish discharge. Mild alkaline douches readily clear up this type of vaginitis. Dr. Doble referred to two cases of ulceration of the genitalia that were cured by the use of an autogenous diphtheroid vaccine.

**The Spirocheticidal Activity of the Human Syphilitic Serum and the Immunologic Significance of the Wassermann Reaction.**—KOLMER and RULE (*Arch. Derm. and Syph.*, 1929, 20, 90) working on experimental rabbit syphilis, mixed suspensions of active *Spirocheta pallida* with the unheated sterile serums from both healthy nonsyphilitic individuals and syphilitic (strongly positive Wassermann) individuals. Control animals received the spirochetal suspensions mixed with saline solution. All the control animals became infected with syphilis while the animals receiving the spirochetal suspensions mixed with human syphilitic or nonsyphilitic serums did not all develop active syphilis. The fresh normal and syphilitic serums appear slightly and equally destructive for *Spirocheta pallida* at 37° C. *in vitro* in an exposure of two hours as compared with a physiological solution of sodium chlorid.

Further experimental studies were done to determine the effect of human syphilitic (strongly positive Wassermann) and nonsyphilitic serums *in vivo* on rabbits with active syphilis. The animals were treated in two groups, one with intravenous injections of syphilitic human serum while the other group received nonsyphilitic human serum. In no instance were there any appreciable curative (spirocheticidal) effects nor a response to the nonspecific effects of serum proteins. No immunity could be obtained by injection of syphilitic human serum into rabbits prior to inoculation with spirochetal suspensions.

The authors conclude that acquired immunity in syphilis is not humoral in character and is not due to demonstrated spirocheticidal antibodies in the serum. Specific serum prophylaxis and treatment of syphilis does not occur nor is it possible by known methods. Syphilitic serum containing large amounts of complement-fixing antibody (strongly positive Wassermann) is apparently devoid of specific spirochetal activity. The presence of the complement-fixing antibody does not denote coincident presence of antispirecheticidal substance but may be an index of tissue immunity.

## GYNECOLOGY AND OBSTETRICS

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**The Present Status of Lead Therapy in Malignant Disease.**—In view of the world-wide interest in the treatment of malignant diseases by means of the injection of lead preparations it is most welcome to the

profession to peruse the report of BLAIR BELL (*Brit. Med. J.*, 1929, i, 431) who is the chief proponent of the method. His report deals with the results obtained from November 9, 1920, to November 9, 1928, and therefore gives a good general survey of the situation. The report is as follows:

1. Total number of cases treated . . . . .	566
2. Died of the disease before treatment could be completed . . . . .	359
(a) Received less than 0.25 gm. of lead . . . . .	198
(b) Received more than 0.25 but less than 0.5 gm. lead . . . . .	161
3. Died of disease after treatment was concluded . . . . .	77
4. Died of intercurrent affections, while under treatment . . . . .	7
5. Died as result of extensive destruction of tissue . . . . .	5
6. Complete treatment refused . . . . .	22
7. Too recent for results to be estimated . . . . .	31
8. Believed cured but died of other affections . . . . .	2
9. Disease completely arrested . . . . .	12
10. Believed cured and treatment stopped . . . . .	51

Bell reminds us that in any estimate of results the serious type of case treated must be clearly remembered; it may be described as consisting largely of that in which the condition was considered hopeless. Ignoring, however, any consideration of temporary benefit, amelioration of symptoms and prolongation of life, it appears that 303 cases have to be considered (items 2 (b), 3, 8, 9 and 10) cases which received more than one-half of the minimum treatment advised. Seventy-seven died after full treatment, consequently it might be argued that there were 65 successes as opposed to 77 failures. Moreover he has reason to believe that at least 40 per cent of the "too recent" cases will terminate favorably. Nevertheless, to put his statistics in the worst possible light, he states that there were 65 successes out of 303 cases treated, that is 21.5 per cent of successful results. He urges the recognition of the following points relative to this form of treatment: (1) No one in his senses would care to suggest that the possession of a knife and a few instruments is all that is required for the surgical cure of carcinoma of the stomach. Yet some seem to think that for lead therapy in this disease all that is required is that lead shall be pumped into the veins of the sufferer. (2) The scientifically minded inquirer will not demand that a new method of treatment for cancer operating on the worst and most advanced types of cases shall give far better initial statistical results than those obtainable with other long established and standardized forms of treatment acting on early and selected cases; but if it should be so, those capable of appraising evidential values will appreciate the vast possibilities that await full and proper development of the method tested.

**Differentiation Between Syphilis and Cancer of the Cervix.**—It is well to remember that in any field of medicine syphilis may have to be considered as an etiologic factor and its ability to mimic various types of lesions has long been known. In the consideration of the differential diagnosis between syphilis and cancer when we are confronted with a lesion on the cervix, GELLHORN (*Am. J. Syph.*, 1929, 13, 1) states that the consistency of the new growth constitutes a very valuable diagnostic criterion. A syphilitic lesion may be soft on the

surface but is always hard or firm in the depth so that the examining finger cannot penetrate deeply. This behavior is due to the fact that in syphilis the connective tissue is infiltrated and, therefore, becomes more resistant. In cancer on the other hand, there is but an apparent hardness, produced by the masses of newly formed epithelial cells, but on continued pressure, the finger can always break through into deeper layers where it encounters a soft spongy tissue. Superficial or deep disintegration is characteristic of a malignant growth. He believes that the color of the lesion is of great diagnostic importance. Syphilitic lesions have a more or less marked yellowish discoloration which is relieved by a reddish undertone, while cancer appears a very deep red to the eye. Chancres and secondary syphilitic ulcers are almost always surrounded by a thin red line caused by new formations of capillaries. If the lesion is separated from the external os by a zone of normal mucosa the diagnosis of syphilis may be safely made. Of course, the microscopic examination usually will make the absolute diagnosis.

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## OPHTHALMOLOGY

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**Iridoavulsion.**—HARDING (*Penn. Med. J.*, 1929, 32, 766) presents a case of complete loss of the iris; it is of particular interest because of the light which it will throw upon the process of accommodation. The iris had been completely torn off by a splinter of glass, so that the ciliary muscle was exposed and the ciliary body and the fibers of the zonule of Zinn could be seen plainly. Even with an ordinary ophthalmoscope it is possible to see that the body of the ciliary muscle distinctly moves forward and the lens approaches the cornea; also the periphery of the lens assumes a slightly mottled appearance which becomes smoother in distant vision. The patient, ten months after the accident, has 6/6 vision and is not bothered particularly by light, though she wears a slightly colored lens.

**Ocular and Surgical Torticollis.**—BRAUN (*Med. Klin.*, 1929, 25, 590) report ocular torticollis showing none of the characteristics of surgical torticollis; degeneration of the sternocleidomastoid muscle; asymmetry of the skull and of the face; inheritability of the trouble and frequent association with other deformities; regular, rapid, cicatricial regeneration of the operatively removed sternocleidomastoid muscle. The position is assumed to restore binocular vision and most frequently results from paralysis of the superior oblique. The head is then inclined to the healthy side, bent slightly forward and turned to the healthy side; thus binocular vision is restored. Should the inferior oblique be

affected, the head is raised, turned to the healthy side and inclined to the diseased side. On the other hand, if the superior rectus is paralyzed the head is raised, turned to the side of the affected eye and inclined to the healthy shoulder. An isolated paralysis of the inferior rectus causes a bending, turning and inclination to the affected side. Treatment consists of tenotomy on the unaffected side of the proper muscle to produce compensation; for instance, if the superior oblique is affected compensation is obtained by tenotomy of the inferior rectus on the healthy side. Surgical and orthopedic measures, such as are used in surgical torticollis are absolutely unavailing. Convergent squint, nystagmus and sometimes improperly corrected astigmatism may also cause ocular torticollis.

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#### **Diagnostic Value of Isolated Pupillary Symptoms in Visceral Syphilis.**

—LURIA (*Deutsch. med. Wchnschr.*, 1929, 55, 1073) states that anomalies of the pupils may appear as an isolated symptom in visceral syphilis and are of importance for early diagnosis since they bear witness of the pleural-visceral nature of the disease. By anomalies of the pupil Luria does not mean those pronounced changes which indicate an involvement of the central nervous system, but slight ones which may be overlooked by the examining physician. Anisocoria, Argyll-Robertson and finally the disappearance of the sharpness and distinctness of the delineation of the iris are all isolated signs which he found variously combined and not rarely only on one side. While anisocoria appears in a number of nonsyphilitic diseases it is far more frequently associated with them. The Argyll-Robertson need not be the sharply pronounced type; lesser degrees of the condition are equally indicative. These signs are particularly excellent since they may be residua of an earlier syphilis being extremely stabile and not yielding to specific treatment; they also may occur in hereditary syphilis.

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**Optic Neuritis and Dental Sepsis.**—SMITH (*Brit. Med. J.*, 1929, ii, 99) reports the case of a man, aged thirty-five years, who came complaining of a "black cloud" in the outer field of his left eye. Examination showed the macula normal, but the nasal edge of the left optic disk was "fluffy." Vision in each eye was 6/6 with correction. Using the Elliot scotometer it was found that the blind spot of Mariotte was much enlarged with snail-track extensions toward the fixation point and one or two isolated scotomata. This, in conjunction with the hazy nerve head, pointed to optic neuritis. Physical examination was negative except for secretion in a tonsil, which was removed. Five days later some color perception was lost and vision had dropped to 6/12. The teeth were rayed and two proved to be suspicious; two others had pyorrhea. The four were extracted. A week later vision had improved to 6/9 and in seven weeks it was 6/6, the optic disk normal and all consciousness of the cloud gone. There can be no doubt of the relation of the dental sepsis to the optic neuritis. Smith also stresses the importance of Elliot's scotometer, since the enlargement of the blind spot and the two small scotomata would have been entirely missed by the ordinary perimeter. Without its use the significance of the slight haziness at the nasal edge of the disk would have been missed.

## OTO-RHINO-LARYNGOLOGY

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**The Asthma-Eczema-Prurigo Complex.**—DRAKE (*Brit. J. of Dermat. and Syph.*, 1928, 50, 407) details an account of 20 skin conditions, all of which were associated with asthma either in the patient or in his immediate family. Of these cases 14 were flexural eczema and 6 were nonflexural in type. The latter group included 1 case of infantile eczema, one case of pruritis with urticaria, one case of lichen urticatus, one nonflexural eczema, and 2 cases of ichthyosis. Most of the cases had septic foci and a small series had definite protein sensitization. All the eruptions associated with asthma were characterized by intense itching which, like asthma itself, is of paroxysmal nature. Most important in the causation, in the belief of the author, is the nervous coefficient or "make-up" of the patient. Underlying the asthma-eczema-prurigo complex is an inherent—or possibly acquired—dysfunction or disharmony of the autonomic nervous system.

**A Positive Symptom of Mastoiditis.**—BERGER (*Ann. Otol. Rhinol. and Laryngol.*, 1929, 38, 1929) calls attention to spasm and rigidity of the upper third of the M. sternocleidomastoideus as a frequent symptom of mastoiditis—especially in children or in adults with thin mastoidal cortices or whose mastoids have been perforated. The spasm and rigidity depend upon the extension of the suppurative process and "are found only when mastoid cells have undergone necrosis." The symptom is elicited best by gently palpating with the fingers of both hands and comparing both sides. It is only of significance when present.

**Scalp Tenderness as an Indication of Dural Involvement in Mastoiditis.**—Having observed that scalp tenderness frequently has been the chief complaint of patients with acute mastoiditis, DIXON (*Ann. Otol. Rhinol. and Laryngol.*, 1928, 37, 1154) has found that this symptom is of value: (1) as an indication for exposure of the dura of the middle fossa at operation; (2) as assistance in selecting the most extensively involved ear in bilateral mastoiditis; (3) as an additional indication for mastoidectomy; (4) in the diagnosis and drainage of an extra dural abscess, and possibly in the prevention of this complication. Patients with unilateral scalp tenderness often complain of shooting pains to the corresponding eye and sharp, intermittent shooting pains deep within the ear of the same side. At operation, the author has been impressed by the marked zygomatic destruction and extensive involvement of the dura of the middle fossa, which he has encountered more frequently in adults over fifty years of age. After a recitation of 6 illustrative cases and of 2 paradoxical ones, Dixon enters upon a

neurologic consideration of the reasons for scalp tenderness in cases presenting middle-fossa dural involvement and states that "it is quite evident that the fifth nerve is intimately connected with the dura of the middle fossa. Also it is a well-known fact that nerves passing through the Gasserian ganglion are quite susceptible to disturbances of sensation."

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**A Study of Acute Infection of the Respiratory Tract in the Ape.**—During an investigation of the type of acute infections of the human upper respiratory tract usually grouped under the term "Common Cold," DOCHEZ, SHIBLEY and MILLS (*Proc. Soc. Exper. Biol. and Med.*, 1929, 26, 562) selected as the animals for investigative purposes the anthropoid apes, inasmuch as they not only frequently suffered from "Common Colds," but that the source of infection was a human being, similarly afflicted. It was found that, during periods of normal health, the upper respiratory flora resembled, in respect to bacteria present, that of the human upper respiratory tract to a surprising degree.<sup>1</sup> During the period of observation a number of the animals contracted upper respiratory infections presumably from chance human contacts and the marked increase in numbers and spread in area involved by the potentially pathogenic bacteria already present in the upper respiratory passages was one of the striking features of the picture. In an attempt to communicate by means of a filterable agent a respiratory infection comparable to the human cold, filtrates of nasopharyngeal washings from early human cases with a "Common Cold" were introduced intranasally into several apes. Of the first 7 animals so inoculated, 3 contracted upper respiratory infections similar in their manifestations to the spontaneous infections of the simian and to the "Common Cold" in human beings. The incubation period of the experimental infection was about thirty-six hours. The nature of the active filterable agent is as yet unknown. From the filtrate in all positive experiments an anaërobic bacillus of the type described by Olitsky and Gates was cultivated.

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**Investigations of Diphtheria Carriers.**—In presenting a statistical study on human carriers of *B. diphtheriae*, KOLLMANN (*Arch. f. Kinderh.*, 1929, 86, 185) found that of 3062 children, 418 (13.6 per cent) harbored the Klebs-Loeffler bacillus in their upper respiratory passages. The carrier state was encountered most frequently in younger children; and in 38 per cent of newborn infants. The number of carriers increased during the winter, spring and autumn; also, among those children living in unhygienic environment, and in those who had gastrointestinal disturbances and pathologic states in their nasopharynges. The incidence of morbidity paralleled that of the carrier state. Most favorable therapeutic response followed isolation and topical application of silver nitrate solution (2 per cent).

<sup>1</sup> Shibley, Hanger and Sachez with the assistance of Mills (*Proc. Soc. Exper. Biol. and Med.*, 1926, 22, 258.) See Retrospect: *AM. JOUR. MED. SCI.*, 1926, 172, 300.

## RADIOLOGY

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**Effect of Ultraviolet Light on the Blood.**—Of thirty-one abnormal cases studied by DORNE (*Arch. Phys. Therap., X-ray, Radium*, 1929, 10, 296) there was a definite decrease of the red blood cells in those cases receiving a general exposure. The white blood cells and lymphocytes were definitely increased in those cases irradiated by the fractional method, and general irradiation produced no appreciable difference. The hemoglobin was slightly increased by both methods. Coagulation time was decreased in 60 per cent of the cases. Blood platelets were increased 100 per cent in every case studied.

**The Visualized Esophagus in the Diagnosis of Diseases of the Heart and Aorta.**—RIGLER (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 563) strongly recommends visualization of the esophagus with barium for roentgenologic examination of the heart and aorta. A very thick barium paste is used, which the patient holds in his mouth, swallowing it only when all preparations have been made. Roentgenoscopic examination is made in the posteroanterior, right and left oblique and right lateral positions. Dilatation of the left auricle is an early and fairly constant sign of mitral disease, and its absence makes a diagnosis of mitral disease very doubtful. Such dilatation or its absence may be proved by examination of the esophagus which is displaced posteriorly and compressed when the left auricle is enlarged. It may also be displaced to the right, rarely to the left. Using the esophagus as the right border, a more accurate transverse measurement of the transverse and descending portions of the aortic arch can be made. Dilatations of the arch will produce deviation to the right and posteriorly and compression of the esophagus. The actual size of an aneurysm can be clearly delineated. Tortuosity and lengthening of the descending aorta, such as occur with arteriosclerosis and hypertension, can be graphically demonstrated by distortion of the esophagus, which accompanies the aorta in its course. Dilatations, either local or general, of the descending aorta produce anterior displacement and compression of the esophagus. If the dilatation or aneurysm is in the proximal three-fourths, there may also be displacement to the right; if in the distal one-fourth, there may be displacement to the left.

**Radiation Treatment of Cancer of the Breast.**—In the experience of PFAHLER and WIDMANN (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 546) recurrent cancers of the breast with glandular and mediastinal metastasis show a postoperative life of forty-five months with irradiation, as



compared with twenty-seven months when surgery alone is used. Inoperable primary cases show an average life of fifty-four months when treated by radiation, as compared with thirty-four months when no treatment is given. In an average of the statistics from ten clinics in which surgery and irradiation were used, 58.3 per cent three-year and 43.2 per cent five-year cures, as compared with the surgical results alone in thirty-two clinics in which there were only 38.6 per cent three-year cures and 28.8 per cent five-year cures. The writers therefore recommend irradiation in all cases of cancer of the breast, with or without surgery, according to the indications.

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**The Effect of Roentgen Rays on the Gall Bladder: Experimental Production of Cholecystitis.**—A definite acute and chronic cholecystitis was experimentally produced by BRAMS and DARNBACHER (*Radiology*, 1929, 13, 103) in a series of dogs with dosage of Roentgen rays that are within the range of those used for therapeutic purposes. The changes produced are destructive. They consist of hemorrhage, inflammatory edema, round-cell infiltration, fibrous tissue hyperplasia, and, in some instances, necrosis of the epithelium, and resemble the type of cholecystitis produced by chemical means. Basing their opinion on the relative lack of injury to the exposed portion of the duodenal and pyloric mucosa, the authors believe that the gall bladder epithelium is comparatively more sensitive to Roentgen ray exposure than the other organs in apposition to it. Hence the possibility of injury to the gall bladder by deep therapy in the region of the right upper quadrant must be borne in mind.

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**Pulmonary Syphilis.**—A case of syphilis of the lung in a woman thirty-nine years of age is reported with illustrations by ALLISON (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 21). Roentgenograms made during an attack of influenza showed a nodular consolidation extending out from the root of the right lung and invading the parenchyma of all three lobes. The shadow of the right diaphragm was faintly visible through a thickened pleura which partially obscured the lower half of the chest. Six months later roentgenograms showed a definite extension both of the pleural thickening and the pulmonary consolidation. The lesion resembled an infiltrative type of Hodgkin's disease. One month afterward, and approximately three weeks after treatment with salvarsan and mercury was instituted, a third set of films showed remarkable resolution of the process. After four months of treatment the lesion had almost completely disappeared.

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**The Effect of Iodized Oils on Serous Membranes.**—From experiments on dogs, GRANDALL and WALSH (*Radiology*, 1929, 12, 499) conclude that lipiodol and lipoiodin are irritating to certain serous membranes. Intrapericardial injection produces pericarditis with effusion, followed by death in about two weeks. Intrapleural injection produces a pleuritis of variable grade; some animals die. Injection into joints produces some inflammation of the capsule. Intraperitoneal injection appears to be harmless. Poppy-seed oil and ethyl brassidate are equally as irritating to the pericardium as their iodine compounds; sesame oil is somewhat less irritating, while olive oil appears to be practically innocuous.

## NEUROLOGY AND PSYCHIATRY

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**Arteriosclerotic Parkinsonism.**—MACDONALD CRITCHLEY (*Brain*, 1929, 52, 23) makes an extensive review of the literature for the purpose of calling attention to Parkinsonian symptoms in connection with the arteriosclerotic syndromes. From this study he arbitrarily divides the entire group into subtypes, Type I being characterized by rigidity, fixed facies and short-stepping gait. Type II is similar to Type I with the addition of pseudobulbar manifestations. Type III is similar to Type I but with the addition of dementia and incontinence of urine and feces. Type IV is similar to Type I with signs of pyramidal disease but without pseudobulbar manifestations. Type V, as Type I, but with superimposition of cerebellar symptoms. He reviews the symptomatology and pathology in great detail and compares the arteriosclerotic syndromes with postencephalitic, senile and idiopathic forms of Parkinsonism. He believes that in association with cerebellar arteriosclerosis, incomplete pictures of Parkinson's disease are more common than complete pictures and all degrees of involvement may occur. The chief differential points between arteriosclerosis and idiopathic varieties are that the arteriosclerotic cases may commence suddenly, although an insidious onset is more usual; the progression is more rapid and may proceed by a series of abrupt exacerbations; the age of onset while approximately the same in the two conditions is of some value, as very early or very late onset is suggestive of a vascular basis; the tremor is usually absent in the sclerotic cases, the muscles feel firmer to the touch and the rigidity is often characterized by a superadded tendency toward catatonia; many of the arteriosclerotic cases show bulbar signs and emotional incontinence or may show a more or less profound dementia; and evidence of focal cerebellar symptoms, of peripheral arteriosclerosis, or of high blood pressure suggests the arteriosclerotic type. The blood pressure, however, may be low in the senile or decrepescient types. The essential pathological features are lesions in the globus pallidus and in the substantia nigra but changes at other levels can be demonstrated as contributing toward the rigidity. He believes that Parkinsonism is a syndrome which may occur under numerous pathological circumstances, depending upon the site rather than the nature of the disease.

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**A Form of Myasthenia Gravis with Changes in the Central Nervous System.**—DOUGLAS MCALPINE (*Brain*, 1929, 52, 6) presents a case of myasthenia gravis occurring in a female, aged twenty-three years. Onset

with dysarthria at twenty-two years, followed by diplopia and fatigability, especially in the evening. A year later she showed physically, bilateral and variable ptosis, diplopia, weakness of the orbicularis oculi and of the lower facial musculature. Fatigue was easily inducible in the soft palate, tongue and limbs. Reflexes and sensation were normal. Exitus after fifteen months of illness in a dyspneic attack. Autopsy showed no gross abnormalities of brain or spinal cord. Histologically the visceral and endocrine organs were normal except that the thymus gland was markedly hypertrophied. Cerebral cortex, subcortical white matter and basal ganglia were normal except for a mucocytic degeneration, especially involving the white matter. Motor nuclei in the brain stem were unaltered except that a few cells at each third nucleus showed slight changes. The vessels were normal. The spinal cord showed marked infiltration of the bloodvessels with round cells and a slight degree of gliosis, especially around the anterior horns, but the motor cells were normal at all levels. Mucocytes were more prevalent in the spinal cord than elsewhere. He considers the possibility of myasthenia gravis being related to epidemic encephalitis but after review of the literature he concludes that no definite relationship is to be demonstrated in any of the cases so far reported. The marked inflammatory reactions evident in his own case he considers to support the idea of such a connection to some extent, especially as mucoid degeneration is more often associated with epidemic encephalitis than with other organic brain diseases. The same considerations lead him to conclude that his own case does not fall into any previously described clinicopathologic group. "It is concluded from a study of the case that there is a form of myasthenia gravis associated with inflammatory changes in the central nervous system, the cause of which is at present problematical."

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**A Case of Relapsing Interstitial Hypertrophic Polyneuritis.**—HARRIS and NEWCOMB (*Brain*, 1929, 52, 108) present a case differing clinically from that of Dejerine and Sottas yet showing the same pathologic picture. The chief difference lies in the recurrent attacks resembling polyneuritis over a period of six years with complete recovery between the attacks. The last attack lasted twelve months with muscular wasting and foot drop and terminal attacks of choking, dyspnea and finally paralysis of the diaphragm due to involvement of the vagus and phrenic nerves. They find no previous case, identical to this, with necropsy, in the literature. They believe that the Dejerine and Sottas type of familial hypertrophic interstitial neuritis should be distinguished as a separate group from recurrent polyneuritis, although the hypertrophic changes found in this case forms a remarkable link between the two groups and both may be due to a similar cause.

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**Death Following Cisterna Puncture.**—PINEAS (*Der Nervenarzt*, 1929, 1, 25) states that very few cases with death following cisterna puncture have been reported. He reports the case of a man, aged fifty-six years, who had been considered as cerebral lues with a negative blood and spinal fluid Wassermann. The Pandy and Nonne tests were both 4+; gold sol 221100; mastic 122200. He had previous lumbar puncture and on August 6, 1927, cisterna puncture was performed with the patient

in the sitting position. The needle was inserted 6 cm. without obtaining any fluid. It was withdrawn and a second needle was inserted about 5 cm., but no fluid was obtained. As an attempt was made to push the needle a little deeper the patient collapsed, so the puncture was abandoned and the patient placed in bed. He had a bigeminus pulse and Cheyne-Stokes respiration. He improved somewhat after the administration of stimulants but died about nine hours after the puncture. At autopsy, they found a generalized chronic vascular change of extreme degree. The vessel walls were greatly thickened, both in the brain and spinal cord. The paths of the two needles were seen in the pia and there was a marked subpial hemorrhage. In varied locations (brachia pontis, the sensory vagus nucleus, and so forth). they found bloody extravasation immediately surrounding the vessels. The vessels of the fourth ventricle were enlarged with very thick walls and bound together in a fibrous mass with the medulla and the cerebellum. At the site of the needle punctures in the pia were two vessels which had been penetrated and extruded blood on pressure. He considers that the chronic changes in the bloodvessels were predisposing factors to the lethal result of cisterna puncture. In spite of the exitus the author considers that the large number of cases that have been successfully performed makes this procedure still desirable but he believes it should be performed with extremely careful technique and even then in some cases may not be entirely free from accidents.

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## PATHOLOGY AND BACTERIOLOGY

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UNDER THE CHARGE OF

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**Researches on the Titer of the Blood Lipase in Different Forms of Tuberculosis.**—MICOLAU and ANTINESCU (*Arch. roum. de pathol. exper.*, 1928, 1, 437) studying the blood lipase in 30 cases of tuberculosis, with especial involvement in different instances of pulmonary parenchyma, bone, serous membranes, and meninges, found the titer of the ferment well maintained in the incipient stages of the disease but considerably diminished in the graver forms of the malady. The more acute types of tuberculosis with meningeal involvement showed little diminution of the blood lipase. It appeared that the lipase titer varied more in proportion with the general state of the disease than with the degree of advancement of a local tuberculous lesion. Its reduction was associated with an unhappy clinical course and unfavorable prognosis. In 9 cases, in which the lipase in pleural, or peritoneal fluids was determined, its titer was approximately half the titer of the serum lipase. The lipase ferment was not found in the cerebrospinal fluid of conditions of tuberculous meningitis, but neither

is its presence demonstrable normally. The lipase occurring in the blood was found to be a serum lipase, as evidenced by its reactions to quinine, atoxyl and sodium fluoride; pancreatic and hepatic lipases were not demonstrable in the blood serum. The resistance of serum lipase to quinine varies with the titer of the ferment, being greater when the lipase is more active while atoxyl and sodium fluoride also inhibit its action.

**Laboratory Infection with *Bacillus Typhosus*.**—Little is known about many of the conditions of infection with the Gram negative pathogenic bacilli of the intestinal tract. The accidental infections in laboratories which have occurred from time to time have been brought together and analyzed by KISSKALT (*Arch. f. Hyg. u. Bakteriolog.*, 1929, 101, 137). The cases from a previous report in 1915 are included and a number of most interesting facts are given. There were 39 cases of infection with pure cultures of *Bacillus typhosus* in which the moment of infection was known. Of these 6 were fatal, 6 very severe, 5 severe, 10 rather severe 8 were mild and in 4 severity was not mentioned. The incubation period of 32 cases varied between three and twenty-one days, and in 14 of the 32 it was under fourteen days. Some of the responsible cultures had been on media for a long time, while others were but recently isolated. The number of bacilli entering the oral cavity was usually large but not necessarily so, and a number of cases are reported in which although the bacilli were taken into the mouth the infection did not follow. This latter type of case is usually kept secret so that the percentage of those receiving the bacilli who became ill cannot be determined. A group of cases in which the infection with pure cultures was most probable, another group in which it clearly appeared to have occurred in the laboratory but in which it was not known whether from cultures, stools or urine, and a third group in which the infection was from either intestinal contents or blood, all add to the interest and value of the report. A number of examples of laboratory infections with other bacteria help to strengthen the impression that laboratory infections are not as uncommon as is generally believed.

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**A Study of Diphtheria Mortality.**—LUCIA (*Univ. of Calif. Pub. Health* 1929, 1, 247) made statistical comparisons of diphtheria mortality in three age groups in relation to conditions of urban and rural populations

and established the following relations: (a) Deaths in the 0 to 4 age group during a year of low incidence are most likely to occur in urban populations, especially in industrial communities, among the illiterates who live under crowded conditions, and where there is concentration of child population. An increase in the number of homes tends to reduce the number of deaths from this disease, as does also an increase in the number of persons engaged in farming occupations. Negroes also correlate negatively with deaths in this age group. During an epidemic, urban population with its accompanying industrialism does not tend to proportionately increase the number of deaths in the 0 to 4 age group. On the other hand, more complete dissemination of the organism produces a higher mortality in rural sections of the country where there are many susceptible children. (b) Deaths in the 5 to 9 age group are more prevalent in cities over 25,000 population in a year of low diphtheria incidence. A high mortality is associated positively with manufacturing industries, child population concentration, and, to some extent, with illiteracy. Where there are many negroes, many homes per unit population, and much farming, the number of deaths is low. During an epidemic year the mortality in this age group increases in cities, and rises in proportion to the number of homes, number of persons engaged in farming occupations, and number of children in the 0 to 4 age group. The number of deaths, however, drops in inverse proportion to the urban population, number of illiterates, and negro population. (c) Deaths in the 10 and over age group in a nonepidemic year occur in direct relation to the number of homes, and in a lesser degree, to the number of persons engaged in manufacturing occupations. There are comparatively few deaths in this age group among illiterates and negroes. During a year of high incidence, the 10 and over age group mortality rises among persons engaged in farming occupations, but drops among those engaged in manufacturing occupations. It remains high in relation to the number of homes. (d) Deaths among all age groups, in a year of low diphtheria incidence, usually occur in relation to urban communities where there are great chances of infection by contact because of overcrowding. Under epidemic conditions, the high mortality shifts from urban to rural communities, when increased dissemination makes possible the spread of infection to the great reservoir of susceptibles in country districts. (e) Better social and economic conditions tend to protect children of the 0 to 4 age group from diphtheria, and thus to build up a large group of susceptibles in the later age groups who suffer high fatalities especially during epidemics. (f) There is a rise in ratio of the number of deaths in the 5 to 9 age group to the number in the 0 to 4 age group across the United States from south to east, and east to west. This rise seems dependent upon the differential effect of certain population variables, for example, number of homes per unit population, illiteracy, etc. (g) The secular trends of the ratios of the number of deaths in the 5 to 9 age group to the number in the 0 to 4 age group are upward in all sections of the country. This tendency may be the effect of the epidemic year of 1921 or it may indicate that, since the 5 to 9 age group is beginning to participate in diphtheria mortality to a greater extent, an increased general diphtheria mortality may be expected. (h) Judging from experience in the large cities of the Atlantic coast, writers on diphtheria tend to stress

artificial immunization of the 0 to 4 age group, rather than of the 5 to 9 age group. It is apparent from this study of mortality that the immunization of school children should not be neglected, at least in the western states. (i) Although the actual number of diphtheria deaths occurring in children of ages 0 to 4 years is greater than in those of ages 5 to 9, a proportionate mortality for the 5 to 9 age group of 16 per cent, as compared with a proportionate mortality for the 0 to 4 age group of 3 per cent, indicates that diphtheria is an important cause of death in the 5 to 9 age group. This is an additional reason for directing efforts toward immunization of this group.

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**Rocky Mountain Spotted Fever. A Preliminary Report on the Weil-Felix Reaction.**—KERLEE and SPENCER (*U. S. Pub. Health Rep.*, 1929, 44, 179) found that the serum of rabbits and of humans suffering from, or convalescent of, Rocky Mountain spotted fever gave a positive reaction with certain strains of the proteus organism. This is a point of similarity between this disease and typhus fever.

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**A Study of the Relationship between Type of Ventilation and Respiratory Illness in Certain Schools of New Haven, Conn.**—GREENBURG (*U. S. Pub. Health Rep.*, 1929, 44, 285) reports studies on 2052 people in mechanically ventilated schools and on 1546 pupils under window ventilation. The results of the observations seem to clearly favor window ventilators, the figures for the latter group showing absences for respiratory conditions about half as large as those for the mechanically ventilated units. The exact cause of this difference was not determined. The conclusion has the following final paragraph taken from the report of the New York State Commission on Ventilation: Because window ventilation is practicable for the ordinary schoolroom it does not follow of course that the assembly room, the theater, and other places seating, in certain cases, many people can also be dealt with in this manner. Each type of inclosure must be handled as a distinct problem. Natural ventilation has its limitations. That the schoolroom is not beyond these limitations is indicated by this study.

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ORIGINAL ARTICLES.

THE INFLUENCE OF RESEARCH IN BRINGING INTO CLOSER  
RELATIONSHIP THE PRACTICE OF MEDICINE AND  
PUBLIC HEALTH ACTIVITIES.\*

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THE three concepts—research, medical practice and preventive medicine—contained in my theme represent three different states of mind. Constant application and time may have indelibly fixed and directed our mental outlook toward one of them. Or the mind in its growth may have risen above this one-phase state and combined in its mental outfit, two or even three of the phases typified by the three concepts. My task, however, is to keep them separate, for it is in the one-track mind that trouble arises from time to time as a result of conflict with the viewpoints external or alien to it. In taking this position I am compelled briefly to define what I understand by the terms public health, medical practice and research and their respective sphere of action. The concept of public health or preventive medicine is relatively new. If we go to the Century Dictionary of 1885 and its later supplements we will not find any definition of public health, although there are such expressions as public holidays, public indecencies, and others recorded. Nor do we find any mention of the expression preventive medicine although other medicines, such as cephalic medicine and logical medicine, are recognized. We do find the term sanitary science established: it is to show how the parasitic and other causes of disease may be avoided.

\* Presented at a meeting of the Boards of Council of the Milbank Memorial Fund, held on March 13, 1929.



Even in the *Encyclopedia Britannica* of 1910 we find statements of public health laws, but nothing to indicate that the terms public health and preventive medicine had become crystallized out in definite form.

The present-day function of the medical practitioner is to relieve and palliate the pains of illness and to restore health. This is best understood if we take into account the evolution of medicine beginning with the dawn of human history. Two ideas seem to have dominated the physician—to ascribe disease to a cause and to search for a restorative remedy. The supernatural causes as interpreted by primitive society were gradually brought to earth and its enveloping atmosphere and last to factors internal and external to the patient himself. Today they are formulated as constitutional and environmental. Among the latter are microbic, dietetic, and other depressive factors. Public health and sanitation developed out of medical practice, its germ being the causal concept of disease, while medical practice became more directly concerned with the task of relieving distress in illness and applying empirically discovered means to restore normality to bodily functions.

Public health is thus the embodiment of the newer concepts of disease which assert that much of routine treatment has been ineffective, and sometimes injurious, and that the growing knowledge of causation forces preventive measures into the foreground. To determine causation and necessary conditions of disease a continuing analysis of disease phenomena is an essential requisite. Hence public health has its foundations in experimental, laboratory research and when it leaves the laboratory it takes its analytical methods into the field. Few epidemics can be traced to their source without the use of laboratory methods.

Research is fundamentally a state of mind involving continual reëxamination of the doctrines and axioms upon which current thought and action are based. It is, therefore, critical of existing practices. Research is not necessarily confined to the laboratory although it is usually associated with an elaborate technique and complex instruments and apparatus which require a laboratory housing. This is controlled research which endeavors to pick out of the web of Nature's activities some single strand and trace it towards its origin and its terminus and determine its relation to other strands. The older type of research involving observation and study of the entire fabric of disease largely with the help of the unaided senses, such as was the practice of doctors a century ago, has had its day, but backed by experience and a keen observant mind it even now occasionally triumphs over the narrow controlled research of the laboratory. It is the kind used by Darwin and other early biologists in establishing on a broad, comparative basis, the evolution of plant and animal life. Research is thus a vital part of

both medical practice and public health activities. It has become the fountain-head of the advances in both preventive and curative medicine. The bedside studies and the refined technique of the laboratory may still exist side by side when they do not clash. Many keen bedside observations are confirmed and reënforced by laboratory technique and many determinations in the laboratory are placed on a firm basis by the great experience of the physician. The technique of both preventive and curative medicine is thus created and remodeled from time to time by medical research. Both functions, though not its direct offspring, have been adopted and nurtured by it. Both are governed by its results in their operations.

When we come to the aims and objects of preventive medicine we find an entirely different motive power. It is the social consciousness and conscience which assumes control. Early public health activities emphasized the protection of the environment of the patient afflicted with a communicable disease rather than the patient himself. But both humanitarian and selfish considerations induced the community in the presence of certain diseases to take full charge of the patient. So we have as outgrowths of chiefly lay public health activities, the infectious-disease hospitals and the sanatoria for the tuberculous, to which both incipient and advanced patients are admitted. This incursion into the domain of the practising physician by bringing under one roof groups of patients affected with the same disease is met by a strong countercurrent from practice into preventive medicine. To appreciate this interchange, we must focus on the principle or doctrine which underlies both activities. This is briefly the projection of the results of civilized man's activities into the future. The idea of sowing and reaping, of planting and harvesting, with a period of patient waiting intervening, enters here. Futurity is an element of all medical practice today. Even in the actual presence of disease, the physician tries to interfere with the spread of the infectious agent in the body, its invasion of new tissues and organs. He tries to keep the virus localized, so as to reduce or prevent later injuries. He holds back secondary and superinfection. He studies the reactive capacities of the patient and tries to give them opportunity for maximum activity. He uses the vaccines and serums of laboratory origin, not necessarily to cure but to prevent further inroads and to mobilize latent capacities. All these procedures and measures have the element of the immediate or more distant future in them. They have almost entirely originated in laboratories devoted to public health, hygiene and sanitation. In brief, the treatment of disease has been gradually losing its character of emergency under the influence of research. The element of time and the natural recuperative capacity of the living tissues are more and more taken into consideration.

Medical practice has furthermore greatly gained in accuracy through the introduction of diagnostic methods of laboratory origin in the examination of blood and discharges. Individuals distributing disease promiscuously are readily detected. The causes of epidemics referable to the consumption of animal products, such as milk, have been brought to light to the benefit of medical practice.

Medical practice and preventive medicine apparently facing one another as competitors at the beginning of the bacteriologic era and getting their impetus from quite different medical theories and mental operations have been gradually drawn together willy-nilly by the force of truth developed by the underlying activities of research. This shows them to be after all of one substance, differentiated only by the points of attack. In the points of attack, however, minor differences become accentuated. Neither side able to see the whole may fall into error from time to time. The organizations devoted to problems of infectious diseases have seen only the microbe. The physician has seen the effects of heredity and special constitution in the variations between individual members of the same family in many reactions toward disease. He had been clinging to heredity in tuberculosis until dislodged by the bacillus, and now he is returning again to a modified view of heredity, with the bacillus in full view however. Preventive medicine looks with dismay on healthy carriers but the physician may regard them as normal. On the other hand, the physician realizes that there will always be disease, either of one kind or another, whereas the public health worker has dreams of completely suppressing infectious diseases.

Public health operations deal with mass phenomena and consequently must use statistics. The physician deals with the individual. Statistics are of little use to him, for his prognosis will probably depend on his own background of experiences. Even when he knows that 95 per cent undergoing a certain operation survive, this does not tell him whether his patient may not be one of the unfortunate 5 per cent. Public health doctrines are simple, but actual disease is very complex. Science seeks the simplest experimental conditions to determine truth, whereas practice inherits all the complications of Nature. The experiment assumes uniformity, the physician accepts diversity in his material. Both views are true in part only and each needs the other as a corrective. Thus diverging views conditioned by the field of work, the method of approaching it and the direction taken in it, lead naturally to a certain lack of appreciation of the respective functions of the other group. We might almost say they are tunnelling from two extremes into the mass of disease. Moreover the appreciation of the great mass of the lay public is often governed by superficial considerations. It has always been difficult to appraise properly the value of preventive

work. The surgeon who successfully deprives a patient of some recalcitrant organ receives more attention than one who should discover infection of drinking water in time to avert an epidemic. The countless casualties and catastrophies that do not happen as the result of anticipatory activities of preventive medicine would make fairy stories ordinary reading. They, however, have only a negative value in stimulating the appreciation of the public. To value prevention demands a sixth sense acquired only by a few. The highest achievement of civilized society is to be able to predict and prophesy and thereby control the immediate future.

That there should be some mutual lack of appreciation, some conflict of opinions between the two wings of the medical army may thus be taken for granted. Mutual criticism is uncomfortable but it is not an unmixed evil. It invites self-examination and correction of defects on the part of the more intelligent and makes for advance. Mere adulation does not involve any severe mental effort, but the discovery of defects implies observation and reflection on the part of the critic. The one who lauds does not need to prove his assertion, whereas the critic may be called upon to demonstrate the precise location of the weak spot he claims to have found. Concerning the relative merits of the two wings of medicine there need be no discussion for, like wings, they need one another to function and the community needs both. One function takes care of the accidents and casualties of life, the other peers just ahead to avoid those approaching. As long as disease prevails, the physician cannot be spared and disease will continue to exist for in the civilized world it, in its gravest forms, simply replaces the violence of Nature in removing the senile and the unfit. The physician is the outpost of the public health army. He is often the first to scent new diseases and to give warning of impending danger when he correctly diagnoses a case unexpected and out of the ordinary. He is the one to discover the spark, but it often requires unusual intelligence to do this sufficiently early. Public health cannot dispense with the supporting aid of practical medicine until the last case of some disease has been detected and restrained. It is the so-called last cases which will give most trouble to all agencies involved. They will be the most difficult to apprehend and the easiest to get out of hand and start new foci of disease unobserved.

It is not infrequently taken for granted that the results of laboratory research are final and its operations infallible. This, however, is far from true. The laws, theories, and inferences of experimental research are as subject to rectification as are inferences based on other human activities. They are approximations getting nearer and nearer the actuality with time. The methods of research may not be in error but the foundations of the experimental enquiries may have been inadequate. All research is based on so-called axioms

and postulates, the ultimate accuracy of which may be called in question and sooner or later subjected to investigation itself. In this way each generation provides more accurate supports. The change which our conceptions of such well-known diseases as diphtheria and tuberculosis have undergone in the past forty years is not easy to grasp because of its gradualness. Yet it is formidable. As long as disease exists, the operations of preventive medicine must be founded on our knowledge of disease. Health means no disease. Disease is the positive pole from which the current of research flows. It is not improbable that we shall be treated to some surprises in concepts of disease in due time which may make it desirable to reverse completely some of our present theories. We are thus forced to admit the fact that all human enquiries are narrow and partial. To include all conditions would require more than the Einstein type of mind to formulate the experimental attack. We must be satisfied with piecemeal work in the hope that occasionally some synthesizing genius will appear who can put the collected fragments together in some form acceptable to us and which will serve as a fresh pattern for further endeavors.

There is still another reason why humility of spirit should hover over our undertakings. In Nature everything is in a flux. Living things are changing. Nature is everywhere trying hundreds of experiments with the opportunities the human race is putting before her through the increasing flux and mobility of man and the things he controls. Out of this trial and error method come new diseases or new adaptations of existing ones. Epidemic flare-ups of well-known diseases come together with such apparently new developments as poliomyelitis, encephalitis and undulant fever. Just how these changes come about rests with future microbiologists coöperating with many other biologic and medical investigators. At present, we can only guess what the ultimate processes are, but it can scarcely be doubted that the ceaseless movement of the race is furnishing the occasions and trial combinations.

It was a happy conception to bring the resources of medical science and practice to play upon certain preventable diseases in a geographically defined community. The demonstration is a great experiment in the natural history of disease and a test of what modern medicine can do. The success of any large scale demonstration depends both upon the relative truth or accuracy of the fundamentals and the thoroughness with which they are applied in practice. If, for instance, the thorough application of what we are supposed to know of such a disease as tuberculosis fails to reduce its incidence in a population there is some unrecognized factor in the etiology. Our fundamentals, in other words, are not sufficiently close approximations to the reality. To demonstrate this would amply compensate for the extra expenditure of energy even if the demonstration was regarded as a failure.

The second requisite for securing the full benefits of a demonstration is the comprehensive and thorough application of the fundamental data in practice. To do this the demonstration must become a connecting link between the two kinds of activities, the preventive and the curative, for it must apply both the results of scientific research and the experience of the individual physician practising in a given territory and supposedly acquainted in general with the natural history of the population and the environmental conditions. It should bring together the student of public health and the local doctor.

The predominant hope involved in demonstrations, as well as the usual measure of success to be attained, is the numerical reduction in morbidity and mortality. We should, however, look somewhat beyond these goals and consider the demonstrations successful only if they teach us something we had not known before, something that can be applied to future experiments of which these are only the pioneers. How not to do a given task often ranks with or above positive instructions. In fact it is on a par with all health practice, the concealed motto of which is, how not to be sick. To insist on a general cleaning up of infectious disease as a result of the demonstration is to anticipate and discount in advance the experiment, for the demonstration is after all a great time experiment with modern concepts of prevention as the real issue. As I stated before, they must come in for test and rejuvenation from time to time in view of the changing condition of the entire world life, human, animal and plant.

Demonstrations are helpful in that they, in addition to their primary tasks, permit some light to play on the economic problems of disease. Though the physician sees them in the intimacy of the household, he has neither the time nor the means to bring his observations as a whole into the open and invite inferences and conclusions useful to the community. This the demonstrations may do if the accumulating material warrants it. It is the demonstration that is most prepared to tell from its special researches in what directions surplus means and energy may be spent with maximum returns in the form of health to the community. Finally, without the voluntary activities of lay groups entering the field of public health and these demonstrations which bring an entire population under the influence, spiritual and physical, of health principles, it would be well-nigh impossible to stimulate the interest of the public and create a so-called public opinion, which in the last resort is our dependence in assisting the inert mass of tradition, medical, legal and lay, to move a step forward.

## OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA\*

### I. THE EFFECT OF THE ADMINISTRATION TO PATIENTS WITH PERNICIOUS ANEMIA OF THE CONTENTS OF THE NORMAL HUMAN STOMACH RECOVERED AFTER THE INGESTION OF BEEF MUSCLE.†

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IT is the opinion of most physiologists and clinicians today that the secretory activity of the stomach is not indispensable to the continued well being and life of the individual.<sup>1,2</sup> This belief is the result of the practical observation that frequently large portions of the stomach, rarely even the entire organ, have been removed in animals and in man without apparent significant disturbance of the processes of digestion or assimilation;<sup>3</sup> and the idea possesses the theoretical basis that the enzymes of the intestine are apparently capable of carrying out for most proteins the digestion necessary to produce amino-acids.<sup>4,5</sup> It is, however, a fact known to clinicians that there are certain abnormal bodily states in which pathologic alterations of the secretions of the stomach may be encountered; and it has been suggested that a deficiency of the secretory function of the stomach might bear a relationship to the associated manifestations of disease.<sup>6,6a</sup> By far the most discrete of the conditions in which the question of the etiologic significance of a defect of the chemical function of the stomach has been raised, is Addisonian pernicious anemia. Since Grawitz<sup>7</sup> and others pointed out just before the beginning of this century the alteration of the gastric secretion, it has become recognized that a practically complete and constant absence of hydrochloric acid and of pepsin is found in nearly all cases of this disease.<sup>8</sup> For this and for other reasons to be given later, experiments on the gastric digestion of patients suffering from

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pernicious anemia were undertaken in February, 1927, and are now described in this paper. The inherent difficulties of exact and prolonged clinical observation have been found great, but have not seemed to render unwise efforts possibly capable not only of shedding light on the cause of pernicious anemia, but also of yielding new information concerning the functions of the human stomach in respect to remote organs; particularly since the observations were of a chronic disorder not so far known to exist comparably in animals.

*Consideration of the Possible Significance of the Achylia Gastrica.* The almost universal incidence of an extreme reduction or absence of hydrochloric acid in the stomach contents of patients suffering from pernicious anemia has been established by the work of many observers.<sup>8</sup> Recently, by the use of new methods, it has become possible to demonstrate that this disturbance in these patients is remarkably great. The stomach of these individuals can be shown to be incapable of secreting acid even under the powerful stimulus of histamin subcutaneously injected;<sup>9</sup> and in contrast to the ability of the normal stomach to secrete various dyes after introduction into the blood stream is the total incapacity in this respect of the organ in pernicious anemia.<sup>10</sup> In a recent review of the literature bearing on the subject of the etiology of pernicious anemia, Cornell<sup>11</sup> concludes as follows: "If one fact has received ample confirmation in connection with the entire subject of pernicious anemia, it is this, *the stomach contents do not contain free hydrochloric acid.*"

That this strikingly abnormal condition of the stomach may play an important rôle in the production of the disease has seemed probable to others.<sup>6</sup> In fact, the question of the relationship of the achylia to the disease has already received much attention in the literature, and accordingly only the most important bits of the accumulated evidence bearing on this matter will be considered.

In the distribution of the disease, there has been noticed in certain instances a notable tendency for it to occur in several individuals of the same family, and to reappear among their descendants.<sup>12</sup> Weinberg<sup>13</sup> has shown that a disproportionately large number of the unaffected members of such families show a reduction of the hydrochloric acid of the gastric contents. Furthermore, it is known on good authority that achlorhydria precedes all other symptoms of the disease, in a few instances by over ten years.<sup>14</sup> In certain individuals, the prolonged use of alcohol has been known to produce in some a temporary, in others a permanent achlorhydria.<sup>6</sup> The occasional appearance of pernicious anemia in association with an achlorhydria in chronic alcoholics is interesting from this point of view. Various clinicians here recognized that pernicious anemia may appear in association with cancer of the stomach in the presence of an achylia,<sup>15</sup> and since it has been possible in our experience to demonstrate the specific reaction of the disease under these circumstances to the liver extract of Cohn, Minot and their



collaborators,<sup>16</sup> it is possible to state with even more assurance that the anemia is of the Addisonian variety, and not therefore due to bleeding or metastases in the bone marrow. Strauss, Meyer and Bloom<sup>17</sup> have recently reported a case of gastric polyposis with achlorhydria which showed a blood picture consistent with pernicious anemia.

The case in DuBois'<sup>18</sup> Clinic of a girl, aged thirteen years, who developed a typical pernicious anemia blood picture with achylia gastrica, is of unusual significance because the "spontaneous" appearance of the disease at this age is exceedingly rare. This little patient showed a typical remission following the administration of the liver extract just referred to; but since vomiting persisted in spite of the improvement of the blood, and since Roentgen rays showed pyloric obstruction, an exploratory laparotomy was performed. The operation revealed a constricting mass of tuberculous glands matted about the pylorus, an obstacle to gastric function that may well have produced the achylia, as in an adult a cicatrizing ulcer or scirrhus cancer in a similar site may do.

A test of the effect of complete lack of gastric juice could obviously be most certainly carried out if the entire stomach were removed. This remarkable operation had been performed in man and reported in the literature up to 1927 only ninety times, according to Miyagi.<sup>19</sup> Only 34 of these 90 patients were the subjects of total removal of the stomach in the anatomic sense, and recovered at least from the immediate effects of the operation. This author points out that strictly defining the performance of total gastrectomy as the ablation of the entire functional secretory portion of the stomach would probably greatly reduce the number of recorded successful attempts, since the technique by which that result could in reality be accomplished, would involve a division of the esophagus above the cardia. The physiologic significance of this requirement for a complete functional extirpation is obvious, since the cardiac end of the human stomach is richly supplied with glandular tissue. Recently Finney and Rienhoff<sup>20</sup> have reviewed the cases of gastrectomy in the literature. It is interesting that of the nine "total gastrectomies," which from the data given may fairly be assumed to have had a complete surgical removal of the stomach and subsequently survived over a year, 2 cases, those of Hartman and Moynihan, apparently developed pernicious anemia.

Hartman,<sup>21</sup> writing in 1921, states that until that date there was only one case of complete gastrectomy reported in the literature in which the subsequent history had been carefully followed for any length of time. That case was reported by Moynihan<sup>22</sup> as having enjoyed a good recovery for three years following the operation, but as then developing a "severe anemia" with which he died within a year. During the year he had one remission under treatment. An autopsy showed the features of severe anemia with the complete

absence of any recurrence of the primary malignant process of the stomach, or other cause for the lack of blood. The case which Hartman reports undoubtedly had a complete gastrectomy for "carcinoma of the cardiac end of the stomach with no glandular involvement," as was reported by the pathologist. He made a good operative recovery, but returned in about a year with gastric symptoms. Two years after operation the patient presented himself with the typical blood picture of pernicious anemia and some evidence of glossitis. A year later, while on a general diet containing, as it happened, some liver, the blood picture was still suggestive of pernicious anemia and the blood count lower. Dennig<sup>23</sup> has recently reported a case in which pernicious anemia with cord symptoms developed ten years after the complete removal of the stomach for a large ulcer. In this case a response to liver feeding was observed. Hurst<sup>6</sup> mentions three other cases of pernicious anemia as developing after total gastrectomy.

It would, therefore, appear that following or in association with a variety of conditions which might conceivably, or which certainly could, in the case of complete gastrectomy, produce a profound disturbance of the secretory activity of the stomach leading to the presence of an achylia, undoubted pernicious anemia has occasionally developed. It is of course possible that this occurrence is merely a coincidence of unrelated diseases, but it is also possible that there is a significant relation. Achlorhydria and even achylia is said to be frequently encountered in cases other than of pernicious anemia, even in normal individuals;<sup>24</sup> and it is apparently true that some cases showing no evidence of pernicious anemia have gastric findings indistinguishable from those invariably found in the patients with fully-developed pernicious anemia. From the work of Bloomfield and of Keefer,<sup>25</sup> however, it is evident that in the majority of instances in the literature the analyses of the stomach contents are not such as would at present be relied upon to exclude the possibility of a secretion of hydrochloric acid under appropriate circumstances. By the use of nonbuffered alcohol test meals, the determination of the actual pH values, and by means of the secretagogue action of the subcutaneous injection of histamin it can readily be demonstrated that many cases showing "no free hydrochloric acid" with older methods will secrete some or even an abundance of acid. Such a result, however, by any method, in cases of Addisonian pernicious anemia is practically unknown. Although it is commonly stated that extensive cancer of the stomach causes an achlorhydria, it is often possible by the use of histamin to develop hydrochloric acid in such cases, and Davidson<sup>10</sup> has used a dye excretion test as a means of distinguishing the achlorhydria of these cases from that of cases of pernicious anemia. It is undoubtedly true, therefore, that the number of cases with "achylia gastrica" which do not have pernicious anemia is less than has been supposed, and, on the other hand,

that the inability of the stomach of the patient with pernicious anemia to secrete hydrochloric acid under any stimulus is profound.

Furthermore, it will be demonstrated in a later paper<sup>26</sup> that the hydrochloric acid alone of the gastric juice has apparently nothing directly to do with the problem of the protection of the individual against a development of the disease. This observation brings into prominence a further defect in the available data, as a result of the failure of most observers to quantitate characteristics of the gastric juice other than its acidity. Although the content of enzyme apparently decreases proportionately to the acid content in most cases, this is not necessarily so particularly, in cases other than of pernicious anemia; and it is a point upon which more actual determinations might be illuminating.

Finally, if for the moment, the cases in which after a complete gastrectomy pernicious anemia has appeared to develop may be interpreted as the result of the operation, it is probable that a time factor of many months is necessary for the development of the disease even in the absence of every bit of functioning gastric tissue. This aspect of the situation has received further emphasis from modern observations of the clinical course of patients with pernicious anemia treated with liver. Those who have continued to ingest adequate amounts of liver have remained well almost without exception,<sup>27</sup> in contrast to the recrudescence of the anemia after varying lengths of time in the cases of a few who have voluntarily discontinued liver therapy. Under these circumstances, the reappearance of the anemia has sometimes been a matter of months.

*Evidence as to the Nature of the Disease Inferred from the Effects of Liver Therapy.* Strangely enough, it is from experience gained in a study of the patients who have had their blood returned to a normal condition by the use of liver that a fact most suggestive of the possible causal relationship of the achylia to the disease, has been brought out. In these patients, in astonishing contrast to the great improvement of the anemia and other features of the disease, is the total lack of any amelioration of the secretory incapacity of the stomach.<sup>28</sup> These individuals, so clearly and remarkably benefited, nevertheless possess stomachs which seem to be permanently unable to secrete hydrochloric acid; and they must, in order to continue to be well, continue to eat adequately of liver. The converse of this situation is afforded by the case reported by Shaw<sup>29</sup> before the advent of liver therapy. In a man severely ill with pernicious anemia, subsequent to a "spontaneous" remission, free hydrochloric acid was found to have reappeared in the stomach contents of the patient, who was well at last report three years later. If it be supposed that the defective function of the stomach is in some way responsible for the disease, the unusual clinical behavior of Shaw's patient becomes comprehensible, as well as the inevitable tendency of the majority of other cases of pernicious anemia to relapse when liver therapy is discontinued.

A consideration, then, of the facts available from the literature dealing with the subject of the relationship of the achylia to the disease, produces the impression that the contention of a causal relationship is at least a plausible one. Hurst<sup>6</sup> has been the chief exponent in the past of a theory of intestinal sepsis with resulting blood destruction, the abnormal bacterial flora being the result of the absence of the sterilizing action of the acid of the gastric juice. It has been difficult to establish the truth of this hypothesis, and it can now be shown that the intestinal flora are unchanged after the patient has returned to a state of health following the taking of liver.<sup>30</sup> Other theories involving modifications of the conception of intestinal infection have not been proved,<sup>31</sup> and all such hypotheses seem questionable in view of the singularly quantitative nature of the response of the patient to the administration of liver or to a few grams of liver extract daily.

It, therefore, becomes desirable to develop, if possible, a hypothesis which includes the new facts derived from observations with liver therapy, and connects the achylia with the causation of the disease. The quantitative character of the response to liver feeding, both in respect to the regularity of the time of the appearance of the improvement in the blood picture, and in respect to its magnitude, suggests at once the possibility of a dietary deficiency disease. It is in this type of disease that the typical recovery following the supplying of a calculable amount of the factor deficient in the food is so immediately and regularly forthcoming, as, for example, in the relief of experimental scurvy or beriberi in animals. That pernicious anemia can be regularly affected in any way comparable to the effect of the daily administration of 200 to 400 gm. of mammalian liver or kidney, by feeding, in the absence of liver or kidney in the diet, any of the known vitamins has not been demonstrated.<sup>16</sup> Furthermore, with the possible exception of Elders'<sup>33</sup> work there is no evidence known to the author of regularly effective treatment with normal diets or diets containing constituents of the normal diets other than liver or kidneys. Elders has stated that diets rich in vitamins and especially in rare meat will slowly benefit certain patients suffering from sprue or pernicious anemia. The experiments to be described in the present communication do not lend support to these observations. Unless, then, it be supposed that certain articles of the normal diet other than liver or kidneys contain the preventive principle in tangible amounts, presumably equivalent to the dose of liver or kidney necessary to maintain a patient in good health after the relief of the symptoms of fully-developed pernicious anemia, it is difficult to conceive of the disease as due to a simple dietary deficiency comparable, for example, to scurvy. The diet of the unaffected majority of persons in those countries chiefly afflicted with pernicious anemia has contained in the past little or no liver or kidneys; and there are indeed many

healthy individuals who eat little or no animal food. On the contrary, in the patient in whom pernicious anemia has once appeared, the normal diet, if lacking in liver and kidneys, seems to have little or no beneficial effect.

*Statement of a Hypothesis Correlating the Achylia Gastrica with the Reaction of the Disease to Liver Therapy.* However, it is not difficult to think of a possible connection between, on the one hand, the strongly suggestive evidence yielded by the quantitative nature of the response of the anemia to liver therapy, that pernicious anemia is a dietary deficiency disease, and on the other, the facts, that have been reviewed, suggesting that the achylia gastrica may play a part in the causation of this malady. An obvious possibility is that a virtual dietary deficiency might be produced in the presence of a diet entirely adequate for a normal individual, by the notable defect in the process of gastric digestion necessarily imposed by the absence of functional gastric juice. Since in these patients a lack of hydrochloric acid is almost invariably associated with a corresponding lack of pepsin, the environment for the peptic digestion of protein, which is the chief apparent chemical function of the normal stomach, would appear to be entirely unsuitable. That this reasoning may not be altogether unsound, is further suggested by the statement of Cohn, Minot and their collaborators<sup>16</sup> that the active principle of liver extracts effective in the treatment of pernicious anemia is probably a nitrogenous base or polypeptid and so conceivably a derivative of protein. Means and Richardson<sup>24</sup> have recently considered the possible theories of the nature of the disease with reference to the preliminary report of this paper.

According to this hypothesis, then, the significant defect in the patient with pernicious anemia is an inability to carry out some essential step in the process of gastric digestion, thus causing a lack of whatever substance is successfully derived by the stomach of the normal individual from his food. If this idea were correct, by substituting some digestive process of the normal stomach for the presumably defective mechanism of the patient with pernicious anemia, it might be possible to affect the patient's disease favorably, thus giving evidence of the relief of a deficiency of gastric function. Since the prominent chemical rôle of the stomach in digestion is usually conceded to be a splitting of protein, the effect of the peptic digestion of protein was first undertaken. An account of these preliminary experiments and their results will now be given.

*Technique of Observations Designed to Test the Hypothesis of the Achylia Gastrica as a Deficiency Disease Producing Mechanism.* In order to avoid as far as possible the introduction of artificial conditions into the experiments, it was decided as a first observation to carry out the digestion of protein in the stomach of a normal man and to introduce subsequently the products of that activity into the stomach of the patient—*Honi soït qui mal y pense*. Since beef muscle contains about 22 per cent by weight of protein, with only

about 3 per cent of fat and 0.3 per cent of carbohydrate, this substance was selected as a convenient source of protein. It was found possible for a healthy fasting subject to eat 300 gm. of nearly raw finely-ground lean beef muscle (hamburg steak) and after a period of an hour to regurgitate, as a result of pharyngeal stimulation, the entire semiliquid contents of the stomach. To this material was then added enough strong hydrochloric acid to give a pH between 2.5 and 3.5, and the mixture placed in the incubator for periods of time varying from six to thirty hours. In the early experiments, half of the material was incubated for six, and half for thirty hours, the pH being kept on the acid side of 3.5 by appropriate additions of strong hydrochloric acid. After incubation, the fully liquefied material was passed through a fine sieve and neutralized to a pH of about 5 with strong sodium hydroxide, and at once introduced into the stomach of the patient by means of a Rehfuess tube. In order to complicate the experiments as little as possible by other digestive action, the material was given in the evening after the patient had fasted for at least six hours, and no food was eaten until an hour after the feeding. The patients were kept on a diet containing no meat, liver or kidneys, but were allowed eggs for breakfast and chicken and fish occasionally.

Radiographic studies of mixtures of barium sulphate with the hamburg-steak meals showed that in the subjects who furnished the normal gastric digestion, about one-third of the meal passed beyond the pylorus within the hour. The material as recovered after vomiting, thus representing the products of the normal gastric digestion of about 200 gm. of beef muscle, was semiliquid, reddish-brown, contained a good deal of mucus, and had an acidity usually in the vicinity of pH 4 to 5. On rare occasions a slight amount of bile was regurgitated. Bacteriologic studies after the incubation period showed a very slight growth of bacteria. A microscopic growth of yeasts and molds occasionally appeared during the longer periods of incubation of the material. Care was exercised that all subjects, who were healthy medical students or physicians, were free from upper respiratory infections. In a few instances, when initiating the procedure, the mere bulk of the material resulted in mild gastric distress and occasionally in vomiting of portions of the predigested material. On the contrary, the relief of persistent nausea or diarrhea was occasionally surprisingly effected by a single administration of this material.

The patients studied in these series of experiments were all undoubted cases of the classical Addisonian pernicious anemia as evidenced by the finding in all of a characteristic blood picture, a complete absence of free hydrochloric acid in the gastric contents, and in most, a glossitis, gastrointestinal or neurologic symptoms. The initial red blood-cell counts varied from 750,000 to 2,700,000 per c.mm., and no patient was utilized whose condition would not warrant the administration for at least ten days of a potentially

negative material. It was at once discovered that as objective evidence of the effectiveness of the material given, could be taken the changes in the blood associated with the feeding of liver and liver extracts described by Minot and his associates<sup>35,36</sup> namely, a prompt, transient increase of the number of immature red blood cells in the peripheral blood stream followed by a progressive increase of the red blood cell-count. Following the administration of effective doses of liver to pernicious anemia patients these authors have shown that, usually before the seventh day of the treatment,

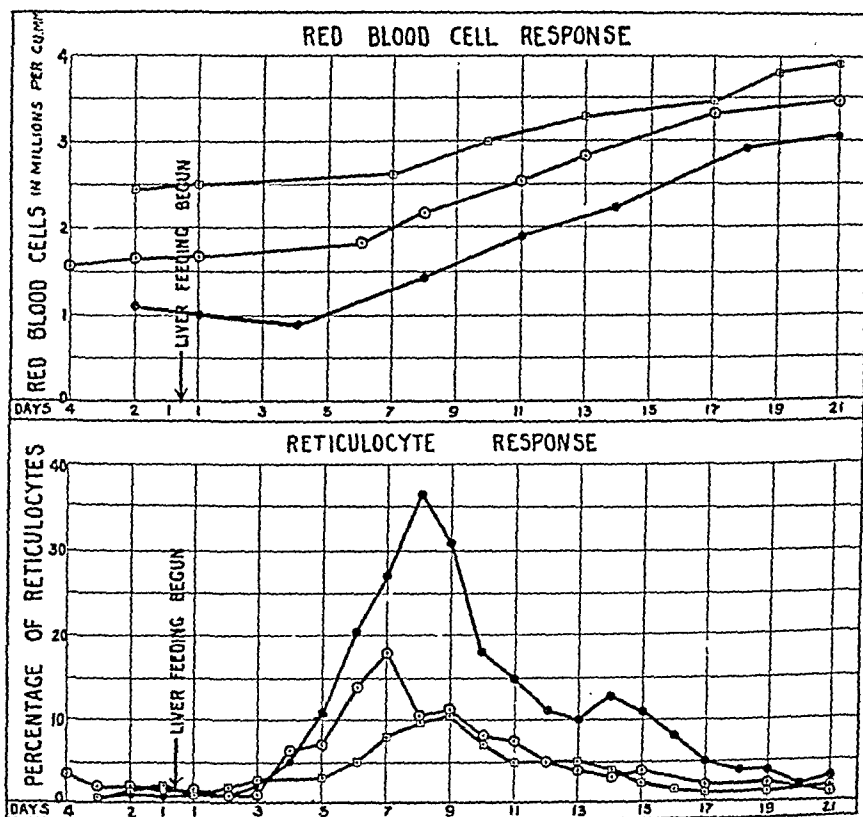


FIG. 1.—The effect on the reticulocytes in pernicious anemia of feeding daily 220 gm. of liver pulp to each of 3 patients with different red blood-cell levels. The same type of line in each part of the figure records data for the same patient. In general, the highest blood-cell count is accompanied by the lowest reticulocyte count and *vice versa*. (Minot, Murphy and Stetson.)<sup>35</sup>

the percentage of reticulocytes (reticulated red blood cells in films vitally stained with brilliant cresyl blue), shows an increase. This percentage progresses to a maximum within a few days and then decreases to approximately the initial value within three weeks. During this period there is a progressive increase of the total red blood-cell count which is at first due entirely to the increment of reticulocytes, but later is the result of new cells without reticulation delivered to the blood stream. A typical illustration of the effect of liver feeding on adult and reticulated red blood-cell values may be

seen in Fig. 2. Smaller but effective amounts of liver will produce a reticulocyte response which does not attain such a large maximum and which may be more prolonged. Indeed, the increase of reticulocytes is a far more sensitive index of improvement than the increase of the total red blood-cell count, since it is possible for the former to appear transiently in response to a feebly potent substance, without any effect on the red blood-cell count whatever being observed. Yet, if any material in uniform daily dosage is effective it is the rule to attain the maximum increase in the reticulocyte percentage usually before the tenth, certainly before the fourteenth day of the therapy. The reticulocyte response is also roughly inversely proportional to the number of red blood cells, as shown in Fig. 1, in patients with

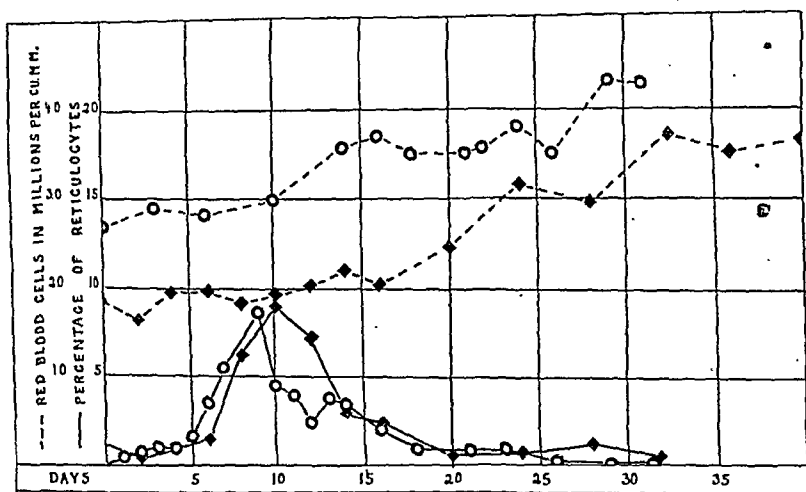


FIG. 2.—The effect on a case of pernicious anemia (Case 1) of the daily administration of the contents of the normal human stomach recovered after the ingestion of 300 gm. of beef muscle is compared with the effect on a similar case of the daily ingestion of moderate amounts of liver. The reticulocyte (solid lines) and adult red cell (broken lines) values of Case 1 (represented by diamonds) are compared with those of the similar case (represented by circles). The reticulocyte responses of both patients are chronologically similar, although the number of reticulocytes produced in Case 1 by the gastric contents is not as great relative to the lower initial red blood-cell count of this patient compared to that of the other patient. An increase of over 1,000,000 red blood cells per c.mm. was observed to take place within thirty days in Case 1.

counts under 3,000,000 per c.mm. Because of the repeatedly demonstrated time relations of this quantitative increase of young red blood cells with successful liver therapy, it may be confidently used to test within a few days the therapeutic properties of any substance, and for that reason has been employed in these experiments. Furthermore, the failure of this reaction to appear within ten days may be taken as evidence of the ineffectiveness of the material given. As additional proof that the patients, who form the basis of these observations, were in truth cases of Addisonian pernicious anemia, may be cited the fact that this characteristic reaction was obtained either with a test substance or later with liver or liver extract of known potency, in every one of the patients.



All blood counts were made from exactly 5 cc. of blood drawn from the arm veins without stasis, and rendered incoagulable by the addition of a drop of a saturated solution of potassium oxalate. As the small dilution factor was invariable no account of it was taken. The vital stains for reticulocytes were made either from the recently drawn oxalated blood after shaking or from a drop of capillary blood. The percentage of these reticulocytes was estimated by counting 500 or 1000 cells, and the maximum percentages were usually checked by another observer.

*The Effect of the Administration of the Contents of the Normal Human Stomach Recovered after the Ingestion of Beef Muscle.* The observations now to be described were made on 10 patients, the entire number of those to whom were given daily the gastric contents of a normal man recovered three-quarters to one hour after a meal of 300 gm. of rare beef muscle. The subsequent incubation with acid, neutralization and administration of this material has been described and the results are tabulated under the heading "test periods" in the table, in which are shown only the blood counts made during the periods of daily administration of the regurgitated material. In 8 of these 10 patients so treated, marked clinical improvement began within a week. A characteristic increase of reticulocytes was manifest by the tenth day and progressed through a maximum. A progressive increase of the red blood cells then followed the appearance of the new elements. Of the 8 patients showing clinical improvement only one, Case 4, treated for only sixteen days, failed to show a gain of over 1,000,000 red blood cells per c.mm. within forty days of the beginning of this manoeuvre. Three of the 8 cases, 1, 2 and 3, showed a gain of 2,000,000 red blood cells in that time. As in the response to liver therapy, the patients with the lower initial red blood-cell counts show the higher maxima of reticulated red blood cells. As an actual basis of comparison, in Fig. 2 is shown the response of the reticulated and adult red blood cells in Case 1 on the same chart with these data derived from a case with a similar initial red blood-cell count, which was treated with moderate daily doses of liver. It will be seen at once that the reactions of both patients are similar.

An inspection, then, of the results set forth in the table shows clearly that a response occurred in 8 of the 10 patients, and was entirely comparable to what might have been expected with moderate uniform daily doses of liver. In 1 of the 8 cases benefited, Case 4, the effect might have been initiated by a coincident transfusion, but the reticulocyte reaction of the patient is quite comparable to that of the other 7, although the discontinuation of the effective material occurred before any increase of the red blood-cell count had appeared. Two of these cases, 5 and 7, showed no perceptible clinical improvement, although in Case 5 at the expected time there was a slight increase of the reticulocytes. These 2 cases, together with Case 6, were treated with material which was transported to another city

TABLE GIVING RESULTS OF ADMINISTERING CONTENTS OF NORMAL HUMAN STOMACH RECOVERED AFTER INGESTION OF BEEF MUSCLE TO 10 CASES OF PERNICIOUS ANEMIA.

CONTROL PERIODS.										
<i>(Daily administration of various substances as indicated below.)</i>										
Days of treatment.	Beef muscle, 200 gm.	Beef muscle, 250 gm.	Beef muscle, 300 gm.	Stomach contents at pH 2.5.	Stomach contents, heated 80° C.	Meat-free diet.	No control.	No control.	Stomach contents, chy. meal.	Beef muscle, pig's stomach, each 200 gm.
	Case 1. R.B.C. Retics. (mils.). (%)	Case 4. R.B.C. Retics. (mils.). (%)	Case 10. R.B.C. Retics. (mils.). (%)	Case 2. R.B.C. Retics. (mils.). (%)	Case 6. R.B.C. Retics. (mils.). (%)	Case 8. R.B.C. Retics. (mils.). (%)	Case 3. R.B.C. Retics. (mils.). (%)	Case 9. R.B.C. Retics. (mils.). (%)	Case 5. R.B.C. Retics. (mils.). (%)	Case 7. R.B.C. Retics. (mils.). (%)
0 . . .	1.86	1.1	2.68	1.03	1.11	2.76	1.0	....	1.54	1.41
2 . . .	1.89	1.5	2.62	0.75	1.13	2.76	0.4	....	1.52	1.63
4 . . .	2.20	3.8	2.58	1.07	1.19	2.70	0.4	....	1.55	1.58
6 . . .	2.41	2.8	2.24	0.75	4.0	2.70	0.3	....	1.48	0.2
8 . . .	1.86	2.4	2.36	0.64	2.0	....	....	....	1.47	1.33
10 . . .	1.88	Transfusion	2.36	0.84	....	2.77	0.5	....	1.38	1.41
2 . . .	1.06	0.5	2.61	0.65	1.19	2.77	0.5	1.57	1.44	1.29
4 . . .	1.96	0.8	2.56	0.80	1.25	2.88	0.8	1.68	1.48	1.12
6 . . .	1.98	0.3	2.48	0.86	1.26	2.95	0.8	1.24	1.56	1.48
8 . . .	1.81	6.4	2.52	0.89	1.42	3.19	7.8	1.33	1.65	1.24
10 . . .	1.92	10.3	2.68	1.10	1.41	3.21	5.5	1.66	2.5	0.86
12 . . .	2.01	7.2	2.69	1.48	7.0	3.24	3.6	1.53	1.42	1.07
14 . . .	2.22	3.1	3.00	1.71	5.2	3.34	7.5	1.39	1.48	
16 . . .	2.54	0.7	3.58	1.87	4.2	3.18	6.4	1.55	1.22	
20 . . .	2.54	2.4	....	2.54	5.4	3.21	3.3	1.84	3.5	
24 . . .	3.16	0.8	....	2.85	1.2	3.64	2.6	1.46	2.8	
28 . . .	2.92	1.4	....	2.66	0.7	3.72	0.4	2.21	4.2	
32 . . .	3.73	0.4	....	2.66	0.8	3.50	....	2.63	7.6	
36 . . .	3.50	....	....	3.05	1.6	3.48	....	2.71	5.6	
40 . . .	3.66	....	....	3.22	0.5	3.88	....	....	....	

TEST PERIODS.  
*(Daily administration of contents of normal stomach recovered after ingestion of 300 gm. of beef muscle.)*

Days of treatment.	Beef muscle, 200 gm.	Beef muscle, 250 gm.	Beef muscle, 300 gm.	Stomach contents at pH 2.5.	Stomach contents, heated 80° C.	Meat-free diet.	No control.	No control.	Stomach contents, chy. meal.	Beef muscle, pig's stomach, each 200 gm.
	Case 1. R.B.C. Retics. (mils.). (%)	Case 4. R.B.C. Retics. (mils.). (%)	Case 10. R.B.C. Retics. (mils.). (%)	Case 2. R.B.C. Retics. (mils.). (%)	Case 6. R.B.C. Retics. (mils.). (%)	Case 8. R.B.C. Retics. (mils.). (%)	Case 3. R.B.C. Retics. (mils.). (%)	Case 9. R.B.C. Retics. (mils.). (%)	Case 5. R.B.C. Retics. (mils.). (%)	Case 7. R.B.C. Retics. (mils.). (%)
2 . . .	1.06	0.5	2.61	0.65	1.19	2.77	0.5	1.57	1.44	1.29
4 . . .	1.96	0.8	2.56	0.80	1.25	2.88	0.8	1.68	1.48	1.12
6 . . .	1.98	0.3	2.48	0.86	1.26	2.95	0.8	1.24	1.56	1.48
8 . . .	1.81	6.4	2.52	0.89	1.42	3.19	7.8	1.33	1.65	1.24
10 . . .	1.92	10.3	2.68	1.10	1.41	3.21	5.5	1.66	2.5	0.86
12 . . .	2.01	7.2	2.69	1.48	7.0	3.24	3.6	1.53	1.42	1.07
14 . . .	2.22	3.1	3.00	1.71	5.2	3.34	7.5	1.39	1.48	
16 . . .	2.54	0.7	3.58	1.87	4.2	3.18	6.4	1.55	1.22	
20 . . .	2.54	2.4	....	2.54	5.4	3.21	3.3	1.46	3.5	
24 . . .	3.16	0.8	....	2.85	1.2	3.64	2.6	1.84	2.8	
28 . . .	2.92	1.4	....	2.66	0.7	3.72	0.4	2.21	4.2	
32 . . .	3.73	0.4	....	2.66	0.8	3.50	....	2.63	7.6	
36 . . .	3.50	....	....	3.05	1.6	3.48	....	2.71	5.6	
40 . . .	3.66	....	....	3.22	0.5	3.88	....	....	....	

following neutralization with sodium hydroxide. The prolonged delay, sometimes as much as twenty hours, before this material could be given to the patients, may have conditioned these two failures, possibly by affording an opportunity for bacterial growth. That these two refractory cases were true cases of pernicious anemia was proved by their entirely typical subsequent reaction to liver extract.

*The Effect of the Administration of Beef Muscle.* Elders<sup>33</sup> has stated that, apparently without liver or kidneys, high meat diets with ample vitamins will slowly improve patients suffering from sprue or pernicious anemia. It was considered theoretically possible that muscle, being of animal origin, might contain, as does liver or kidney, a certain amount of the effective principle. In order to ascertain whether the effect seen in the first group of patients was not simply due to the ingestion of substances already present in the meat before it was introduced into the normal stomach, the following observations were made. Considering that the purely physical effects of fine division involved in the predigestion of the meat might make more available to the patient's use some substance already present, to three of the patients in the first group just described were given daily 200 or more grams of lean beef muscle at pH 5. This meat was as finely divided as possible by passing it through a special meat chopper used in the preparation of liver pulp, or by passing it three times through the usual "Universal" type machine with a fine cutter. It was then mixed with enough water to give it a semiliquid consistency, giving a product of approximately pH 5. This material prepared from 200 gm. of beef muscle was given daily to Case 1 in divided dosage between meals. In a similar fashion Case 4 took 250 gm. daily, and Case 10, 300 gm. of beef muscle daily prepared in the same way. Clinically these cases were not only not improved but said they felt progressively worse. Case 4 suffered from loss of appetite and had some diarrhea despite frequent doses of paregoric. An inspection of the data given in the table under the heading "control periods" shows that there was no significant change in either reticulocytes or total red blood cells; certainly nothing in any fashion comparable to the effect of the administration of similar or smaller amounts of beef muscle given daily in subsequent "test periods" to the same patients after the beef muscle had been received into and recovered from the stomachs of normal fasting men.

It may be objected, however, that the "control periods," being only ten days in length, are not sufficiently long to test the possible low potency of the meat. In these experiments, however, it is the difference between the test and the control periods which it is desirable to observe; and in the experience of Minot<sup>35</sup> and others, the first four days of any ten-day period give ordinarily, even while an effective liver extract is being administered, no evidence of its activity, but must be considered as a continuation of the effect of

any immediately preceding test period of ten days. In these 3 cases, then, the first four days of the "test period" immediately succeeding the "control period" likewise evidence no changes in the reticulocytes and hence give a period of days sufficient to give assurance of the essential inability of lean meat alone to confer any benefit under these conditions. It is to be remembered, however, that it cannot be assumed from these observations that such a diet carried on for months might not be in some way very slowly beneficial as Elders has claimed.<sup>33</sup> These experiments, however, lend no confirmation to his statements, and certainly give evidence that there is no substance already present in raw lean meat which can give effects comparable to those demonstrable in a subsequent period with that amount of meat after a sojourn in the normal stomach. This effect, therefore, necessarily suggests a significant difference between the action of the stomach of the patient and that of the normal man.

**Discussion.** The foregoing experiments clearly demonstrate that the stomach contents of a normal man recovered during the digestion of a meal of beef muscle and subsequently incubated with additional hydrochloric acid contain a substance capable of causing remissions in certain cases of pernicious anemia comparable to those produced by moderate amounts of liver. It was also shown that beef muscle given directly to these same patients had no effect under the conditions of these experiments. This certainly means that no preformed constituent of the beef muscle could have been the basis of the effect seen after recovery of the beef muscle from the normal stomach, and implies either the direct action of some constituent of the secretions produced by the normal man or some action of these secretions on the meat.

The original hypothesis as to the nature of the disease, of course, necessitates for its proof the demonstration of an action of the gastric juice on the food. The foregoing experiments do not afford a basis of discrimination between these two possibilities, since the observations are consistent with either a direct activity of the normal gastric juice or its indirect action on the beef muscle to produce activity. Because both the highly cellular liver and kidney of the healthy animal are known to contain a water-soluble substance effective in the treatment of pernicious anemia, it appeared quite possible that the secretion of the cell-filled mucosa of the stomach might contain a plentiful amount of a similar soluble and effective constituent, obtained incidentally in the gastric juice recovered from the normal stomach with the beef muscle. If this were true the experimental evidence could not then be used to support very strongly the idea of a unique capacity of the normal stomach to produce in some way from the food of the normal man his supply of preventive substance for pernicious anemia. In the event of a subsequent demonstration of the effectiveness of gastric juice alone, it could only be suggested that the stomach alone of all the organs of the body could secrete a substance perhaps later stored in the

liver or kidney, since this demonstration would, of course, give no proof of the stomach as the original source of the effective substance. On the other hand, if it could be shown that the gastric secretions themselves were ineffective unless allowed to come into contact with the beef muscle, clear evidence of a method of producing a preventive substance from an external source would be at hand, and a step taken toward the proof of the original hypothesis as to the mechanism of the disease. Experiments upon this point are reported in the following article of this series.<sup>26</sup>

The demonstration of the ineffectiveness of finely-divided beef muscle itself in causing remissions does more than eliminate the muscle as a source of the substance causing the effects. It bespeaks an important difference between the stomach of the patient and of the normal man, suggesting that it is possible for the latter to respond in some way to the presence of the beef muscle with the production of an effective substance. The stomach contents of the patient, on the other hand, are thus shown not to contain in the presence of the beef muscle a detectable amount of the effective substance, which can apparently be produced in considerable amounts by the normal man under these circumstances and made available to the patient by transference to his stomach. Again, however, it is apparent that the significance of this negative demonstration depends mainly on whether it can be shown that the positive ability of the normal stomach depends on an action of gastric juice upon the beef muscle and not on a direct action of the gastric juice itself.

**Summary and Conclusions.** 1. A consideration of the existing facts concerning the achylia gastrica of Addisonian pernicious anemia, together with the recently acquired knowledge of the effects of liver therapy, leads to the conception of the disease as possibly due to a deficiency of a new type.

2. A working hypothesis has been developed which postulates that the development of the disease is dependent upon an inadequate gastric digestion of protein, thus permitting the development of a virtual deficiency in the face of a diet adequate for the normal man.

3. The results of observations designed as a preliminary test of this hypothesis are reported and are believed to be consistent with it but not necessarily to prove it.

(a) To each of 3 cases of pernicious anemia was given daily for a period of ten days between 200 and 300 gm. of finely-divided raw beef muscle without demonstrable effect on the blood formation during a total of fourteen days.

(b) Immediately thereafter to each of these 3 patients and to 7 others were given daily the incubated contents of a normal human stomach recovered after the ingestion of similar quantities of beef muscle. In the 3 patients mentioned, and in 5 of the 7 others, comprising in all 10 patients so treated, there appeared before the tenth day an increase of the immature red blood cells followed by a

progressive improvement of the anemia entirely similar to that ordinarily observed with the daily ingestion of moderate amounts of liver by similar patients.

4. It is concluded, therefore, that in contrast to the conditions within the stomach of the pernicious anemia patient, there is found within the normal stomach during the digestion of beef muscle some substance capable of promptly and markedly relieving the anemia of these patients.

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## OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA

### II. THE EFFECT OF THE ADMINISTRATION TO PATIENTS WITH PERNICIOUS ANEMIA OF BEEF MUSCLE AFTER INCUBATION WITH NORMAL HUMAN GASTRIC JUICE.\*

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It has already been demonstrated that in the incubated contents of the normal human stomach removed during the process of

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digestion of beef muscle there is present a substance which is similar to mammalian liver or kidney in its ability to produce remissions in the disease pernicious anemia.<sup>1</sup> It has also been shown that beef muscle fed as such to pernicious anemia patients did not produce such an effect. These observations were considered to be consistent with, but not proof of, the hypothesis that the obviously defective peptic digestion of the patient with pernicious anemia might be the basis of a virtual dietary deficiency in the presence of a diet adequate for the normal man.

There are, however, two general ways in which these results may be explained quite consistently with the recognized physiologic differences between the stomachs of the patients and those of normal individuals: (1) it is possible that some substance present in the secretions of the normal stomach, quite independently of the ingested beef muscle, might be the basis of the effects observed. The hydrochloric acid and the pepsin of the normal gastric juice are the chief substances found lacking in the stomach of the patient with pernicious anemia; but the cell-rich mucosa of the normal stomach might be, like the highly cellular mammalian liver, the source of a water-soluble extract secreted in the gastric juice and possessing properties similar to those that may be readily prepared from liver;<sup>2</sup> (2) however, the possibility exists, which is consistent with the original hypothesis, that gastric juice to produce these effects must in some way act upon the beef muscle.

An additional step toward the proof of the original hypothesis would then be taken, provided the first of these alternatives could be eliminated. If it could be shown that gastric juice secreted in the absence of beef muscle or other food is inactive, but that on being brought into contact with beef muscle, itself already shown to be inert, a potent substance was produced, the original hypothesis would be further substantiated. Experiments designed to test this possibility will now be described.

*The Effect of the Administration of Human Gastric Juice Alone and after Incubation in Vitro with Beef Muscle in the Presence of Hydrochloric Acid.* A solution of the problem of securing adequate amounts of fresh active human gastric juice secreted entirely apart from any food substance was found with the use of subcutaneous injections of histamin phosphate.<sup>3</sup> The normal fasting subject was injected with a dose of histamin phosphate in sterile salt of between 0.5 and 0.75 mg. By means of a Rehfuß tube and syringe the gastric juice was removed as fast as secreted for a half hour, following which another injection of histamin was given and the gastric juice collected for another half hour. The average subject under these conditions secreted about 150 cc. of a colorless, or occasionally somewhat bile-tinged liquid containing some mucus. This fluid was then filtered through compress cloth and kept in the ice box until needed. The juice was active proteolytically, and had a free hydro-





chloric acid content of from 40 to 50 cc. of tenth normal hydrochloric acid, with a total acid content of about 10 cc. more of tenth normal hydrochloric acid per 100 cc. of gastric juice. In the experiments to be described, the daily contribution of one or two individuals collecting gastric juice for one hour was used each day in the treatment of each patient. The 10 patients comprising this group were all clinically cases of Addisonian pernicious anemia by the criteria mentioned in the preceding paper.<sup>1</sup> The studies of the blood were conducted as therein described, and the effectiveness of the substances administered was judged on the basis of the response of the reticulocytes and total red blood-cell values<sup>4</sup> as discussed in the same paper. In the table are shown the results of the experiments on the 10 patients of this group.

It was desired first to test the effect of gastric juice alone. Accordingly, to Case 11 was given in the control period a daily average of about 300 cc. of the pure gastric juice. An inspection of the reticulocyte data during this ten-day period shows no significant change and the red blood-cell count remained essentially stationary. The patient said that he felt a little better toward the end of the observation and seemed perhaps to have a slightly better color, but in the next four days no new cells appeared in the blood films. We may then fairly conclude that in this patient 300 cc. of the gastric juice given daily for ten days was virtually ineffective.

The procedure in this case was now changed so that every day 200 gm. of finely divided beef muscle, after thorough admixture with 300 cc. of gastric juice from the same normal subjects, was incubated at 37° C. in a glass beaker with occasional stirring for a period of two hours. The acidity of the mixture was maintained at a pH between 2.5 and 3.5 by sufficient additions of strong hydrochloric acid. At the end of this incubation period the liquefied contents of the beaker were passed through a fine wire sieve, neutralized with strong sodium hydroxide to pH 5, and given without inconvenience by a Levin gastric tube to the fasting patient. It is to be noted that the methods of this incubation *in vitro* with fresh gastric juice are identical with those employed in the *in vitro* phase of the digestion of the regurgitated beef muscle.<sup>1</sup> In marked contrast to the negative results just obtained in this patient with pure gastric juice alone was the striking effect of the incubation of the gastric juice with the beef muscle. There followed prompt clinical improvement and an appearance of reticulocytes in the peripheral blood stream, reaching a maximum of 11.4 per cent on the seventh day of this treatment. There was a progressive increase of the patient's red blood-cell count from 1,376,000 to 2,640,000 per c.mm. in a period of eighteen days.

This experiment is confirmed in its essentials by the observations on Cases 19 and 24. In the control periods of these 2 cases 150 to 200 cc. of gastric juice secreted after histamin were incubated re-

spectively with commercial casein and with a protein prepared from beef muscle after solution of the muscle in strong sodium hydroxide. The products of these incubations did not produce a remission as is now known because of the improper nature of the protein used; but the evidence is presumptive that the gastric juice employed would have been similarly ineffective alone. In the subsequent test periods of these 2 cases, incubations of similar quantities of gastric juice with 200 gm. of beef muscle produced reticulocyte maxima of 30.2 and 13 per cent respectively, as quantitative evidence of the remissions obtained. In Case 24 an increase of from 1.53 million to 2.54 million, and in Case 19 an increase of from 0.74 million to 2.43 million red blood cells per c.mm. were observed to take place in twenty days.

These three experiments strongly suggested that some action of human gastric juice was capable of producing from 200 gm. of beef muscle, known itself to be without effect,<sup>1</sup> a substance capable of causing a remission in pernicious anemia quite comparable to the action of 150 gm. of prepared liver. There still remained, however, the possibility that the combination of gastric juice and beef muscle was effective, not from any essential mutual interaction, but merely from a summation of substances already present in each separately. Even if each contributed a subliminal quantity, together they might, without interaction of any sort, contain initially a total amount of effective substance sufficiently great to be detected. Such might even conceivably be the cause of the remissions seen when the two substances were recovered, necessarily together, from the normal human stomach during the digestion of the meat or after incubation together *in vitro*. Accordingly, further experiments were undertaken in order to settle this point and to confirm if possible the positive results of the *in vitro* incubation of the beef muscle with gastric juice as described in the treatment of Cases 11, 19 and 24.

It was desired to give in a control period to the patients separately the same amounts of the two individually ineffective constituents of the combination, which after incubation together *in vitro* had been found effective. In order to reproduce as far as possible the conditions existing during the incubation of a mixture of the gastric juice with the beef muscle in the presence of hydrochloric acid, to be carried out in the subsequent test periods, each of the materials was to be incubated *separately* for two hours in the presence of hydrochloric acid and then neutralized with strong sodium hydroxide to pH 5 just before administration to the patient at *separate times*. The natural reaction of the hydrochloric acid content of the gastric juice, usually between pH 1 and 2, was the acidity of the incubation period of this substance. In the management of Cases 16 and 17 sufficient dilute hydrochloric acid was added to the finely ground beef muscle to give a pH of between 2.5 and 3.5; in Cases 12, 13 and 15, the beef muscle was merely suspended in water during the

incubation period at pH 5. In order to give separately during the control period the same amounts of the two substances, gastric juice and beef muscle, that were to be given during the test period after incubation together, each patient received daily for at least ten days during the late afternoon and evening 250 to 300 cc. of the incubated gastric juice prepared as above described, and during the morning and early afternoon 200 gm. of the finely ground incubated beef muscle.

In the test periods immediately subsequent to these control periods similar quantities of pure gastric juice, usually from the same subjects were thoroughly mixed with 200 gm. of beef muscle and the material placed in the incubator. There it was allowed to remain for two hours with occasional stirring, at an acidity of pH 2.5 to 3.5, maintained by appropriate additions of strong hydrochloric acid. At the end of this incubation period, the liquefied contents of the beaker were passed through a fine wire sieve, neutralized with strong sodium hydroxide to pH 5, and given by Rehfuess tube to the fasting patient. It will be noted that this procedure is identical with that already described for Cases 11, 19 and 24 during the test periods.

The total quantity of both the gastric juice and beef muscle taken by these five patients during any day or given number of days of both the control and the test periods was therefore identical; and the conditions of incubation as far as possible were the same except for a slightly more acid reaction of the separately incubated gastric juice and except for the omission of the hydrochloric acid in the separate incubation of the beef muscle during control periods of Cases 12, 13 and 15. The significant difference between the two periods was, however, that during the control period these two substances were *incubated and administered separately* to the patient, but *incubated together and necessarily so administered* during the subsequent test period. *Therefore, any differences between the action of the patients during the control and test periods must necessarily be due to the effects of the interaction of the two substances: gastric juice and beef muscle.*

The complete data from all blood examinations made while the 5 patients of this special group were the subjects of the experimental procedures are presented in the table. It will be seen there that Cases 12, 13 and 17 showed during the control period no evidence of a significant increase of reticulocytes. There was no evidence of an increase of the red blood-cell count and no detectable clinical improvement in these patients. In fact, in Cases 12 and 13, there was a distinct increase of the anemia together with other symptoms. The condition of these two female patients was unfortunately complicated by the presence of a cystitis. In the case of Patient 12 the clinical condition did not improve in the test period; and during the test period of Case 13 there was a slight but perceptible rise of

the reticulocytes to a maximum percentage of 5.2 on the seventh and eighth days. There was with this no increase of the red blood-cell count during fourteen days—a result which may be obtained with small reticulocyte increases due to liver extract of low potency.<sup>4</sup> It became obvious, however, when after only a few days of the test periods had been completed and it appeared advisable to begin treatment with liver extract, that these 2 patients, presumably from the effects of the complicating cystitis, could not react satisfactorily even to maximum dosage with liver extract known to be effective. The refractory character of Case 12 was thus clearly demonstrated, and the poor response of Case 13 in the test period was explained. Unfortunately, nothing as to the relative potency of the materials administered in the control and test periods of Case 12 can be inferred.

An inspection of the data compiled from Case 17, however, leaves no doubt of the significance of the interaction of the gastric juice and beef muscle during their incubation *in vitro* in reproducing the effects already seen in the test periods of Cases 11, 13, 19 and 24. On the contrary, during the ten-day control period there was not the slightest evidence of clinical improvement in this patient. The red blood-cell count remained stationary and the reticulocyte percentage showed no significant change, even though the patient was daily ingesting *separately* 200 gm. of beef muscle previously incubated for two hours with hydrochloric acid, and between 250 and 300 cc. of similarly incubated fresh human gastric juice. A few days after this patient began to be given daily the same quantity of these substances incubated *together* in the presence of hydrochloric acid, however, subjective improvement was noted. An increase of reticulated red blood cells appeared in the circulating blood on the fifth day of this regimen and reached a maximum of 15.2 per cent on the twelfth day. During the twenty-two days of this treatment the red blood-cell count rose from 1.52 to 3.08 million per c.mm., and there was a corresponding increase of the patient's color, appetite and activity. Quite of this nature was the clinical improvement seen during the test periods of the other cases of this type, Cases 15 and 16. As will be seen by inspection of the table, these patients showed during the test periods ample evidence of the objective changes in the reticulocyte and total adult red-cell counts which are seen with liver feeding in moderate amounts.<sup>5</sup> In both instances a gain of 1,000,000 red blood cells per c.mm. was produced within twenty-one days by the material digested *in vitro*.

In the control periods of these 2 cases, 15 and 16, a repetition of the negative results of the control period of Case 17 is not seen. There is in the reticulocyte data of Case 15 evidence of a very slight rise; and in Case 16 a pronounced rise to as high as 15.6 per cent appeared on the thirteenth day of this prolonged control period. However, in the subsequent test periods, it became obvious that the beef

muscle and gastric juice after incubation together were distinctly more effective than these constituents of the test material given as far as possible separately. Case 15 attained a subsequent maximum reticulocyte percentage of 8.6 even at a red blood-cell level at which only slightly over 10 per cent was to be expected with the extract from 400 gm. of liver daily.<sup>4</sup> Patient 16 also showed a second reticulocyte rise during the test period. This phenomenon is characteristically encountered, according to Minot,<sup>5</sup> if the uniform daily administration of an effective liver preparation is followed at a short interval by a uniform daily administration of a larger dose of the same, or a similar amount of a more potent material. Here it may be confidently regarded, by analogy with the same phenomenon in observations on cases treated with liver extracts, as indicative that the effectiveness of the material administered in the test periods of these cases was greater than that given in the control periods.

Although it cannot be stated with certainty that the beef muscle and gastric juice would both invariably be inactive under the conditions of the control periods of these experiments, if it were possible entirely to exclude the chance of contact between these two substances within the patient, nevertheless this appeared to be the case in the control periods of Patients 17 and 13. In Case 15 the evidence of an effect during the control period is tenuous, but in Case 16 there was an undoubted effect. A consideration of the experimental conditions necessarily imposed by such conduct of the control periods as was here carried out, suggests at once an explanation for these variations. It was of course possible to be certain of the complete lack of contact between the beef muscle and the gastric juice only up to the moment of administration to the patient. Although given at times as widely separated during any one day as was reasonably possible, there still existed a definite chance for interaction between these substances in some portion of the gastrointestinal tract of the patient. It was hoped that the combined incubation of the test periods would provide a sufficiently great opportunity for interaction in contrast to the absence of any such contact *in vitro* in the control observations, so that a difference amounting even possibly to an absence of an effect in the control periods would be observed. This was realized in 2 patients, 13 and 17; and in the other 2 cases reacting in the test period clear evidence of an effect greater than that seen in the preceding control period was observed.

In further confirmation of the regularity with which the incubation of gastric juice has been found to produce an effective substance from beef muscle, are presented in the table the data from 2 more cases, 14 and 18. Case 14 had no control period but showed in the test period a maximum reticulocyte production of 16 per cent on the eighth day, and an increase of the total number of red blood cells from 1.28 to 2.68 million per c.mm. in 16 days. Case 18 was given 200 gm. of raw spleen pulp daily without effect during the ten days preceding

the test period. In the test period an excellent remission appeared as a result of the administration of the products of the incubation of the beef muscle with gastric juice. A maximum figure of 14 per cent of reticulocytes appeared on the eighth day with an increase of the total red blood-cell count from 1.45 to 2.98 million per c.mm. in twenty days.

Of this group of 10 cases of pernicious anemia, given daily during a test period the results of the *in vitro* incubation of 200 gm. of beef muscle with from 150 to 300 cc. of human gastric juice at pH 2.5 to 3.5, 9 of the cases showed an effect qualitatively similar to the effect of the ingestion of liver or effective liver extract. Fig. 1 shows clearly that in 8 of the 9 cases the effect of this therapy in producing reticulocytes was equivalent to that of 135 to 225 gm. of prepared liver daily.<sup>5</sup> In 7 of the 9 cases this therapy was continued sufficiently long to produce increases of over 1,000,000 red blood cells per c.mm. by the end of twenty days. In the 2 cases complicated by a cystitis and consequently showing a poor response to maximum dosage with liver extract of known potency, there were respectively no response and a poor response.

**Discussion.** From the observations made on this group of patients it would appear that an interaction between beef muscle and fresh human gastric juice produces from these two completely or relatively inactive constituents some substance capable of causing the appearance of a characteristic remission in certain cases of pernicious anemia. That in order to produce this effect an interaction of the gastric juice and the beef muscle is essential is evidenced by the fact that the gastric juice alone was shown to have no effect, and that from previous observations<sup>1</sup> the inactivity of beef muscle alone has been demonstrated. In the present series of experiments, it was shown that if the two constituents of the reaction are treated individually as far as possible, just as is to be done during the subsequent period of their effective interaction *in vitro*, but are kept separate and separately administered to the patient, there is either no effect or no effect of a magnitude comparable to that resulting from their subsequent free interaction.

Since the effect of this incubation of the gastric juice with beef muscle *in vitro* was quantitatively similar in 8 of the patients so treated to that observed in 8 of the previous series of 10 patients to whom were given the contents of the normal human stomach recovered during the digestion of beef muscle (Fig. 1), it seems reasonable to assume that the similar results of the two types of experiments represent an identical process carried out entirely as an *in vitro* reaction in the present instance. In the previous series of experiments,<sup>1</sup> it was shown that beef muscle itself was inert in terms of these reactions. In the present series, the ineffectiveness of gastric juice has been established, and thus the possibility of its direct action as a water-soluble extract of a highly cellular organ has

been excluded. Only the alternative of an action of the gastric juice on the beef muscle remains. It appears proper, therefore, to conclude that in the normal human stomach during the act of digestion of beef muscle there is formed by some action of the gastric juice on the meat a substance capable of markedly relieving the anemia and improving the clinical condition of those suffering from pernicious anemia. It is believed that this effect demonstrates for the first time a relationship of the human stomach to the function of the bone marrow. The general improvement in the sense

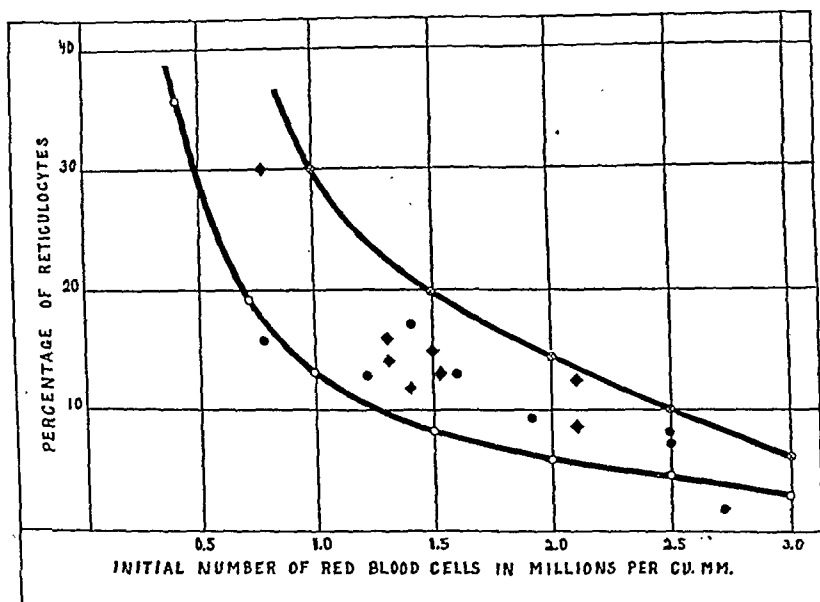


FIG. 1. —The respective maximum percentages of reticulocytes produced in 8 cases of pernicious anemia by the daily administration of the contents of the normal human stomach recovered one hour after the ingestion of 300 gm. of beef muscle are plotted (circles) against the initial red blood-cell counts of these patients. For 8 other cases similar data are recorded (diamonds) as a result of the daily administration of the products of the incubation of 200 gm. of beef muscle with from 150 to 300 cc. of fasting normal human gastric juice secreted after the subcutaneous injection of histamin. The upper curve represents the usual maximum reticulocyte percentages produced by the feeding of about 225 gm. of prepared liver daily to cases of pernicious anemia. The lower curve shows the usual effect of about 135 gm. of liver fed daily to cases of pernicious anemia. It will be seen that the respective maximum on 16 cases treated either by *in vivo* or *in vitro* digestion of the beef muscle with human gastric juice fall in the main between these 2 curves.

of well being, appetite, body weight, and activity of these patients, suggests an important effect on the general metabolism. The striking influence of a remission in one of these patients on the blood cholesterol has been reported elsewhere.<sup>6</sup>

In contrast to this is the demonstration from observations on 3 of the patients of the first group<sup>1</sup> that no comparable reaction can be obtained by administering to patients with pernicious anemia, under conditions most favorable to digestion and absorption, finely ground beef muscle in large amounts. Since it has been shown in



the present series of experiments that the positive effect depends upon the action of the normal gastric juice upon the meat, it seems possible to explain the ineffectiveness of the meat administered as such to pernicious anemia patients by the well-recognized deficiency of their gastric juice. As it is exceedingly difficult to secure any considerable quantity of the gastric secretions of patients with pernicious anemia, no attempt was made to carry out an *in vitro* experiment comparable to that performed in the present group of cases with normal human gastric juice. It was considered that the more significant experiment of the two had already been carried out *in vivo* by feeding beef muscle directly to the patient.

A possible objection to the validity of this experiment, considered to show the inability of the patient with pernicious anemia to produce an effective substance in his own stomach might be raised, since the feeding of beef muscle to the patient directly precluded the possibility of a period of *in vitro* digestion. However, the beef muscle was fed in small amounts in a fine suspension most favorable to any digestive action, and potential gastric digestion was not interrupted by removal of the material from the stomach. In one experiment not reported in these papers hydrochloric acid was added to the meat before its administration to the pernicious anemia patient with equally negative results. Even if it could be shown that under the most favorable conditions of a prolonged *in vitro* digestion a certain amount of the effective substance was formed by the action of the gastric secretions of the patient, the significance of the demonstration of the ineffectiveness of the gastric secretions under conditions actually existing in the stomach of the patient during the development of the disease would not be set aside. Conceivably, also, without the *in vivo* experiment, in the event of a negative result, an objection to the *in vitro* process on the grounds of some unknown artificiality could be raised. It seems proper, therefore, to consider this experiment valid in support of the contention that there is a striking difference in the ability of the stomach of the normal man and that of the pernicious anemia patient to produce the effective substance.

Since much attention has been directed to the possible rôle of the absence of hydrochloric acid in the production of this disease, it seems worth while at this stage of the observations to point out that the effects seen cannot be due to this substance alone or to its individual action on the beef muscle. In the experiments on those patients to whom were given separately in the control periods gastric juice and beef muscle after incubation with hydrochloric acid, there was either no evidence of a reaction in the control period (Case 17), or evidence of a significantly greater reaction when the beef muscle was incubated with both hydrochloric acid and gastric juice (Case 16) in the subsequent test period. (See table.) If the

hydrochloric acid itself had been the sole basis of the effect seen in the test period, a similar effect should have appeared in the control period. On the other hand, there is evidence that a large amount of hydrochloric acid may actually prevent in some way the action of the effective substance. An inspection of the data in the control period of Case 2 of the first series of experiments<sup>1</sup> shows that until the hydrochloric acid added during the incubation of the gastric contents *in vitro* was partly neutralized (pH 2.5 to pH 5) before administration of the material to the patient, no effect occurred. On changing the reaction of the material to pH 5, by the addition of sodium hydroxide, a remission was at once forthcoming in the test period. In the next paper of this series, further evidence of the negative effect of hydrochloric acid itself upon beef muscle will be presented.

The evidence from these experiments is thus quite in accord with the conception of pernicious anemia as a deficiency disease resulting from an inadequate digestion of protein imposed by the obvious lack of gastric juice of the pernicious anemia patient. It is clear that the normal individual can produce during the gastric digestion of beef muscle some substance which by transference to the stomach of the pernicious anemia patient will alleviate the symptoms of the disease. If it may be assumed that the quantitative nature of this effect and that of liver feeding is evidence of a deficiency disease, it is certainly reasonable to assume, as in other deficiency diseases, that the administration of the substance that will relieve the disease once developed will be able to prevent originally the development of the disease. By this reasoning, Addisonian pernicious anemia stands revealed as, in all probability, a disease dependent for its production in the last analysis upon the plainly defective gastric juice of the patient, which is incapable of elaborating the preventive substance shown in these experiments to be formed by the action of normal gastric juice on beef muscle. Since this substance is produced under conditions obviously permitting the peptic digestion of protein, it is possible that lack of this action is the intimate nature of the defect. Experiments designed to throw further light on this problem will be reported in the next paper of the series.

**Summary and Conclusions.** 1. The validity of the hypothesis that the development of the disease pernicious anemia is dependent upon an inadequate gastric digestion of protein, thus permitting the development of a virtual deficiency in the presence of a diet adequate for the normal man, has been further examined.

2. The results of the following experiments are considered to add greatly to the probability of the hypothesis.

(a) To 3 cases of pernicious anemia were given daily 150 to 300 cc. of incubated gastric juice secreted by fasting normal men after histamin injection. In 2 of these cases the gastric juice was incubated

for two hours with an indifferent protein, and in none of these patients was there evidence of effect on blood formation within fourteen days.

(b) To 4 cases of pernicious anemia were given daily for ten days in the afternoon 300 cc. of incubated fasting gastric juice secreted under histamin stimulation, and in the morning 200 gm. of beef muscle, incubated in 2 of the cases with hydrochloric acid, and in the other 3 with water. In 2 of these cases no effect on blood formation was observed within fourteen days. In 1 case a slight effect occurred and in another a distinct effect on blood formation was observed. However, in all of these cases a much greater effect was seen when similar quantities of gastric juice and beef muscle were incubated together. In a fifth case, complicated by cystitis, no effect was seen with either set of conditions.

(c) To the 8 cases just referred to and to 2 others were given 150 to 300 cc. of fasting human gastric juice secreted under histamin stimulation, incubated in the presence of hydrochloric acid at pH 2.5 to 3.5 for two hours with 200 gm. of beef muscle. In all but 2 of these 10 cases an effect upon blood formation was observed comparable to that seen with the similarly treated normal gastric contents in the first series of patients. Before the tenth day, there appeared an increase of the immature red blood cells followed by a progressive improvement of the anemia comparable to that ordinarily seen with the daily ingestion by similar patients of from 135 to 225 gm. of prepared liver. (Fig. 1.)

3. It is concluded, therefore, that by some interaction of normal human gastric juice and beef muscle, both of which have been shown to be individually ineffective, a substance can be developed which is capable of promptly and markedly relieving the anemia of certain patients with Addisonian pernicious anemia.

4. Since it has been shown in the experiments reported in the first paper of this series, that the presence of beef muscle in the stomach of the patient with pernicious anemia is incapable of developing such an effective substance, the conception of the absence of this effect as being due to the defective quality of the gastric secretion of the patient is strongly suggested.

5. It is believed that the correlation between the production of an effective substance and the presence of a normal proteolytically active gastric juice in contrast to the demonstrable lack of both in the patient with pernicious anemia, adds strength to the validity of the original hypothesis of the particular nature of the disease.

6. It is believed that for the first time a relationship between the stomach and the function of the bone marrow of the human being has been demonstrated; and the general belief that the integrity of the stomach is unnecessary to proper body metabolism brought into question.

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## WHAT IS THE RISK OF INSURING APPLICANTS WITH PEPTIC ULCER?\*

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IN order really to answer the question expressed in the title I should first of all be a trained actuary and then I should have at my disposal records extending over fifty years and showing when and exactly why 1000 men and women with definite duodenal or gastric ulceration died. Unfortunately, I am not an actuary and the follow-up data at my disposal are anything but complete. Under the circumstances, all I can hope to do is to give you such impressions as a clinician can obtain as he studies his patients, and such information as he can derive from the answers to questionnaires.

Because it is so hard to keep in touch with many of the persons who have passed through our hands we have to learn much of what we know from the stories of those who, when they come to us, have already suffered for from five to forty years; in other words, we try to get some idea of the future by looking into the past. One of our greatest handicaps in this study is that modern gastrointestinal diagnosis and surgery date back only fifteen or twenty years, and hence no matter how carefully we search we cannot expect to find many patients with ulcer definitely localized in duodenum or stomach before 1910 or 1915. Remember that it was in 1908 that

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W. J. Mayo pointed out the importance of the pyloric ring and showed that more ulcers are to be found caudad to it than orad. Remember also that the first roentgenoscope to be made in quantity in America was shown at the Panama Pacific Exposition in 1915. My first one, secured in 1912, had to be imported from Vienna.

In order to begin, let us imagine that 100,000 men and women of all ages applying for insurance, have experienced some indigestion. Possibly half of them, or 50,000 will have so little distress or so little spare cash that they will never consult a physician. Some will prescribe for themselves, some will consult a druggist, a chiropractor, or an osteopath, and some will trust to Christian Science and other forms of faith healing. Many in this group will doubtless suffer with peptic ulcer and never know it. My reason for making this statement is that the pathologist who is particularly interested and who will look carefully, will often find the puckering scars of duodenal ulcer, and when he questions the relatives he will sometimes be unable to obtain evidence that the deceased ever complained of indigestion.

Robertson and Hargis found such scars in 6.1 per cent of 2000 bodies examined at The Mayo Clinic. This figure is almost twice that representing the incidence of gastric and duodenal ulcer as diagnosed by our roentgenologists (3.3 per cent of 71,675 patients registered in 1926). From England, Souttar reports that 4.3 per cent of 30,000 patients admitted to the surgical wards of the London Hospital were suffering with ulcer.

Robertson and Hargis found active ulcers in 12.8 per cent of the bodies, but this figure does not throw light on the problem before us, first, because the material studied does not represent a fair sampling from the community, and second, because so many of the lesions were probably recent and due to the serious illness that produced the death of the patient. Ulcers or scars were found in 378 of the bodies examined. If we exclude the 163 cases in which an operation for ulcer had been performed, we will have 215 or 10.7 per cent (of the 2000) in which an ulcer or scar may have been found accidentally. As 21 per cent of the gastric and 40 per cent of the duodenal ulcers were healed, active ulcers must have been found unexpectedly in, at the most, 7.4 per cent (of the 2000) and scars in 3.4 per cent. The figure 3.4 is the one which I think should interest us particularly in this discussion because it gives some idea of the percentage of men and women in America with healed ulcers.

In Robertson's experience ulcers are found commonly (in decreasing order of frequency) in association with diseases of the thyroid, the kidney, the prostate (commonly associated with destruction of the kidney), the gall bladder, the brain and cord, and the appendix.

Incidentally, this brings up a point which should be of interest to the insurance examiner when he is appraising the risk of an applicant who has or has had trouble with peptic ulcer. Such persons, and

especially the women, are likely to have other forms of disease in the abdomen for which they may eventually be operated on, and every such operation naturally carries with it a risk. Some idea of the frequency of these complications of ulcer may be seen from Table I. Such tables would be much more enlightening if the surgeon would always examine the gall bladder and appendix and record his impressions in regard to them, but this he is often loath to do, especially when he is hurrying to complete a difficult resection of the stomach.

TABLE I.

	Duodenal ulcer, surgically demonstrated.						Gastric ulcer, surgically demonstrated.					
	Men.			Women.			Men.			Women.		
	Cases.	Totals.	Per cent.	Cases.	Totals.	Per cent.	Cases.	Totals.	Per cent.	Cases.	Totals.	Per cent.
<i>Gall bladder disease:</i>												
"Normal" . . . . .	40			58			35			29		
"No stones" . . . . .	17			3			8			24		
Not described . . . . .	11			24			39			22		
		68	68		85	61		82	77.3		75	71.5
Drained previously . . . . .				4								
Removed previously . . . . .	2			5			2			5		
Removed here: Stones . . . . .	2			15			1			3		
No stones . . . . .				10								
"Cholecystitis" . . . . .	6			3			3			2		
Stone present, not removed . . . . .				1			2			4		
Wall thickened markedly . . . . .	1						1					
		11	11		38	27		9	8.5		14	13.3
Wall thickened . . . . .	2			4			4			4		
Wall thickened slightly . . . . .	3			6			2			4		
Perihepatitis . . . . .				1						1		
Adhesions about gall bladder . . . . .	8			6			3			3		
Contracted gall bladder . . . . .	1											
Large glands on common duct . . . . .	1											
		15	15		17	12		9	8.5		12	11.4
"Not examined" . . . . .	6									4		
		6	6				6	6	5.7		4	3.8
Total cases . . . . .		100			140			106			105	
<i>Appendectomy:</i>												
Done previously . . . . .		13			39			13			24	
Done here with operation on ulcer . . . . .		71			44			50			34	
<i>Pelvic disease:</i>												
Not operated on . . . . .					11						9	
Operated on . . . . .					19						22	

All we can say from the records available is that definite gall bladder disease was present in at least 8.5 or 11 per cent (8.5 with

duodenal ulcer and 11 with gastric ulcer, Table I) of the men with ulcer and in from 13.3 to 27 per cent of the women (Table I). As one would expect from the propinquity of gall bladder and duodenum, cholecystitis was found more frequently with duodenal than with gastric ulcer.

It is impossible to say how much real disease of the appendix there was in these patients but the records show that by the time they were operated on for the ulcer, 13 per cent of the men and from 24 to 39 per cent of the women (24 in the group with gastric ulcer and 39 in the group with duodenal ulcer) had submitted to appendectomy. That these figures are somewhat higher than normal is shown by the fact that Blackford found that 13 per cent of 1000 patients who consulted him in regard to indigestion had parted with the appendix. In women many appendices are removed at the time of operations on the pelvic organs, and in the group of 244 women with ulcer which I studied, from 19 to 22 per cent had submitted to operation for pelvic disease.

But to return to the hypothetical group of 50,000 men and women who are going to physicians because of indigestion: can we make any guess as to the number who are suffering with peptic ulcer? I think we can. At The Mayo Clinic in 1926, 13.7 per cent of the 15,000 patients examined roentgenologically on account of indigestion were found to have duodenal deformities interpreted as due to ulcer, 1.5 per cent had gastric ulcer and 0.3 per cent had ulcers in both stomach and duodenum. If these percentages were the same in the hypothetical group, there should be 6850 with duodenal ulcer, 750 with gastric ulcer and perhaps 150 with gastric and duodenal ulcer. Actually these figures are probably too high because so many persons with particularly resistant ulcers come to us from far distant places and thus interfere with the evenness of the sampling from the Middle West where we get most of our patients. This error may be compensated, however, by the fact that we doubtless fail to diagnose many ulcers.

Statistics which I gathered several years ago show that the average practitioner, unaided by expert roentgenologists, will make the diagnosis in only one-third of these cases. The insurance examiner is likely, therefore, to hear of only 2580 cases of ulcer in the group of 100,000 instead of the 16,000 or more in which he ought to be informed of the presence of the disease.

What now is going to happen to the 2580? Before I attempt to answer this question I must first emphasize the importance of distinguishing between those persons with duodenal ulcer and those with gastric ulcer. As will be shown later the mortality rates are different and the problems of treatment are different.

**Treatment of Duodenal Ulcer.** Turning first to a consideration of duodenal ulcer I will remind you that there are four main types of treatment commonly adopted. The first and probably the most

common, even among physicians suffering with ulcer, is treatment by neglect. In the early stages of the disease the results of such treatment are often good and so far as is known, perhaps just as good as those obtained by careful treatment. Some of my confrères will doubtless be shocked at this statement but I have some statistical data which indicate that it is true. It must be noted, however, that I said "in the early stages of the disease." Unfortunately, in perhaps half of the cases (I have no way of estimating this figure more exactly) the disease eventually becomes so severe and so resistant to ordinary home treatment that something more must be done.

The second form of treatment is an ambulant one in which the patient stays at work and takes food and perhaps alkalis every two hours. It works well in many cases and commonly gives prompt relief. The problem in ulcer, especially in the early years of the disease, is not so much to give relief: this is often easy; the difficulty is to prevent recurrences. The third form of treatment requires hospitalization and careful dieting, and the fourth requires the help of the surgeon.

**Medical Treatment.** Now what chance is there for permanent cure under the various forms of medical treatment? I cannot say because most of the follow-up studies so far made cover periods of only a few years. The recent report of Blackford and Bowers indicates that the intervals of relief after careful hospital treatment are no longer than those secured after ambulant treatment, and this agrees with my own impressions. The statement that in their experience the end results of medical treatment are as good as those after surgical treatment is somewhat surprising but to a certain extent it agrees with the observations of others. It does not mean, of course, that surgical treatment with its greater risk and suffering and expense should be given up. We cannot give it up because in a large percentage of cases the time comes when medical treatment no longer brings relief and the patient finds himself incapacitated and exhausted by suffering. The ulcer has perhaps perforated into surrounding tissues, it is bleeding, or it has mechanically closed the outlet of the stomach. Under such circumstances surgical help must be invoked. That the surgeon fully recognized the limitations of his work and the possibilities of cure under medical care is shown by the fact that often he will refuse to operate until several attempts at medical treatment have been made or until the patient is definitely handicapped by the disease.

I shall not attempt here to review much of the literature on the remote results obtained with the medical treatment of peptic ulcer, because the subject has already been so well discussed in Chapter XLIII of Crohn's book on "Affections of the Stomach." He concludes that if the patient is young and in the first stages of the disease good immediate results can be obtained in three-fourths of



the cases. The difficulty is that these persons do not stay well and actually, the longer one keeps in touch with a group of them the more discouraged one gets.

In Einhorn and Crohn's series of 100 cases carefully treated in the medical wards of Mt. Sinai Hospital and followed from one to four years, the immediate results were excellent, and 86 were apparently cured. Most of them went six months without symptoms, but by the end of the first year 31 per cent of the 86 were back again with the same old trouble. With each succeeding year more cases had to be transferred from the list of the cured to those of the relapsed until by the end of four years, the two groups were about equal. Furthermore, by this time nineteen out of the original 100 patients had turned to the surgeon for relief. Of the group of 22 patients who were observed for the full four years, 7, or 32 per cent, were operated on.

Of the whole group 3 died, 1 of cancer of the lung, another of pulmonary tuberculosis, doubtless aggravated by the severe ulceration of the stomach, and 1 from perforation of the ulcer. Einhorn and Crohn could then, at the end of four years, claim only 27.3 per cent of apparent cures after careful hospital treatment. If they had included the cases in which improvement was noted, the figures would have been 90 per cent for the first few months and 50 per cent for the four years.

Results similar to these have been reported by Barford in England and by Smith in Scotland. Smith, who groups gastric and duodenal ulcers together because he says they are so hard to differentiate, reports that 24 per cent of the men and 8 per cent of the women treated medically had later to be operated on. Interesting from the insurance point of view was the fact that 21 per cent of the men and 19 per cent of the women were eventually so incapacitated by the disease that they were unable to work. In addition there were 16 per cent of the men and 12 per cent of the women who had to turn to lighter jobs.

Forsyth, chief medical officer of a British Assurance Society which makes a specialty of life and health insurance for physicians, has published some figures which, while few in number, are of unusual interest and value because the subjects were almost all physicians, because half were operated on and half not, and because with a sickness-indemnity provision in the policies the company was able to keep a record of recurrences and of the amount of disability suffered. Unfortunately, the insured were observed for periods of only from one to twelve years.

Of the 59 in the series, 22 or 37 per cent relapsed from one to seven times. Fifty-six per cent were operated on, apparently most of them during the period of observation. The number reporting recurrences was practically the same in the two groups but the number of relapses for each person was a little larger in the group treated medically. One such relapse took place as late as ten years

after the apparent cure of the disease. Four of the 33 treated surgically had to have secondary operations: one of them after sixteen years. Two of those operated on died in the hospital and one more died later. Forsyth concludes from this that persons with duodenal ulcer may perhaps be given life insurance but they certainly should not be given sickness insurance.

**Bleeding.** Aside from the risks of operation the two accidents that may cause death in these patients are hemorrhage and perforation. Most observers agree that from 15 to 30 per cent of persons with ulcer will at some period of the disease bleed severely; but fortunately in only about 1 per cent of all the cases of ulcer does such bleeding cause death. According to Barford, in England, bleeding is six times as common with duodenal as with gastric ulcer, but according to Moynihan it is three times as frequent with the gastric lesions. According to Balfour (1927), gross hemorrhage occurred in 18 per cent of 1072 cases of duodenal ulcer operated on. This bleeding was six times as frequent in men as in women. Gross hemorrhage was seen in about 20 per cent of the cases of gastric ulcer.

**Perforation.** Many ulcers perforate but only a small percentage break through the wall of the stomach or bowel so rapidly that gastric contents can soil the peritoneal cavity. When the symptoms are promptly recognized and an operation is immediately performed most of these patients recover. In Scotland, Smith found perforation was responsible for 2.8 per cent of deaths in all types of ulcer. According to Moynihan perforation is half again as frequent with gastric as with duodenal ulcer. Gibson studied 60 cases of acute perforation. Twenty-eight were in cases of gastric ulcer and 32 were in cases of duodenal ulcer. If in his material there was the usual ratio of 8 duodenal ulcers to 1 gastric it must be that the gastric lesions are seven times more subject to perforation than the duodenal. The mortality in the gastric cases was 21 per cent and in the duodenal 12 per cent.

**Surgical Treatment.** As I have already intimated, a considerable number of patients with duodenal ulcer should be operated on as soon as they are seen by the consulting gastroenterologist. Others should accept surgical help only after the inefficacy of medical treatment has been demonstrated. What then will be their chances of recovery?

With a really expert surgeon the immediate mortality should be small, and if the usual operation of gastroenterostomy is performed all but 2 or 3 out of 100 patients should walk out of the hospital. Unfortunately such a low mortality is secured only with surgery at its best and the actuary dealing with this problem will have to allow for the possibility of a much larger percentage of loss after operations.

In the five years following operation the chances of cure or

considerable improvement appear to be between 70 and 90 per cent. Balfour reported, in 1925, that 88 per cent of 1000 patients with duodenal ulcer, operated on ten or more years before, were relieved. In 1927, he reviewed the results in a group of 100 physicians operated on. This study is particularly enlightening because the subjects were all fairly intelligent and all competent to appraise the degree of relief obtained. Their average age was forty-seven years and the average duration of symptoms was thirteen years, so it will be seen that most of them belonged in that group of patients in whom medical treatment is usually of little avail. It was all the more cheering, therefore, to find that after intervals averaging eight and a half years, 84 could report a satisfactory result. Six more, while not entirely relieved, believed that the operation had helped and that it had been worth while. Five had been operated on again, 2 for recurring hemorrhage, 1 for reactivation of the ulcer and 2 for gastrojejunal ulcer. Some of those finally obtained relief, and only 5 of the original group remained unimproved. Similar results have been reported from England by Moynihan, Walton and Broster.

Fremont-Smith and McIver at the Massachusetts General Hospital have recently made a valuable study of the results obtained after operation on 393 patients with duodenal ulcer and 261 with gastric ulcer, observed for periods ranging up to ten years. I will discuss at this point only their results with duodenal ulcer. The immediate mortality was 7.6 per cent, and 4.6 per cent more are known to have died since leaving the hospital. Eighty per cent of the 261 patients watched for a year reported good results. Recurrences soon began to appear, however, and more and more cases had to be transferred from the list of the cured to the list of the relapsed.

Figure 1 shows that the percentage of patients with severe recurrences rose gradually from eight at the end of the first year to nineteen at the end of six years. After that it appeared to drop off a little. The figures suggest that if a patient operated on for duodenal ulcer can get past the sixth year without a recurrence his outlook will be good. If he has had recurrences by this time the chances are that these are going to incapacitate him more and more as years pass. There is some hope also that the patient with gastric ulcer will be fairly safe if he gets past the eighth year without recurrence. We know that reactivations take place after intervals of ten years but we cannot say yet how common they are.

We must conclude, then, that even the best of surgical treatment will not entirely erase that remarkable tendency to recurrence, perhaps hereditary,\* which is seen in a number of patients with

\* Smith found that in 8 per cent of the men and 12.7 per cent of the women with ulcer one or both parents and one or more brothers or sisters were similarly affected. Reich has described a family with peptic ulcer appearing in four generations. At The Mayo Clinic we have the impression that this tendency is more marked in the Jew than in other racial strains and at times it is seen strikingly in the nervous, high-tension, go-getter, sales-manager type of man.

ulcer. No matter what is done for them the disease flares up again and again, and some have to go from one operation to another. This is particularly true of that group of unfortunates who are subject to the formation of chronic gastrojejunal ulcers—perhaps 2 per cent of all who submit to gastroenterostomy.

In spite, however, of all these difficulties and dangers, the careful follow-up study by Balfour and Hunter of 1651 persons with duodenal ulcer, operated on and watched for periods averaging 3.4 years showed that the mortality was a little lower than that of a control group of men and women with a similar age distribution, observed for the same length of time.

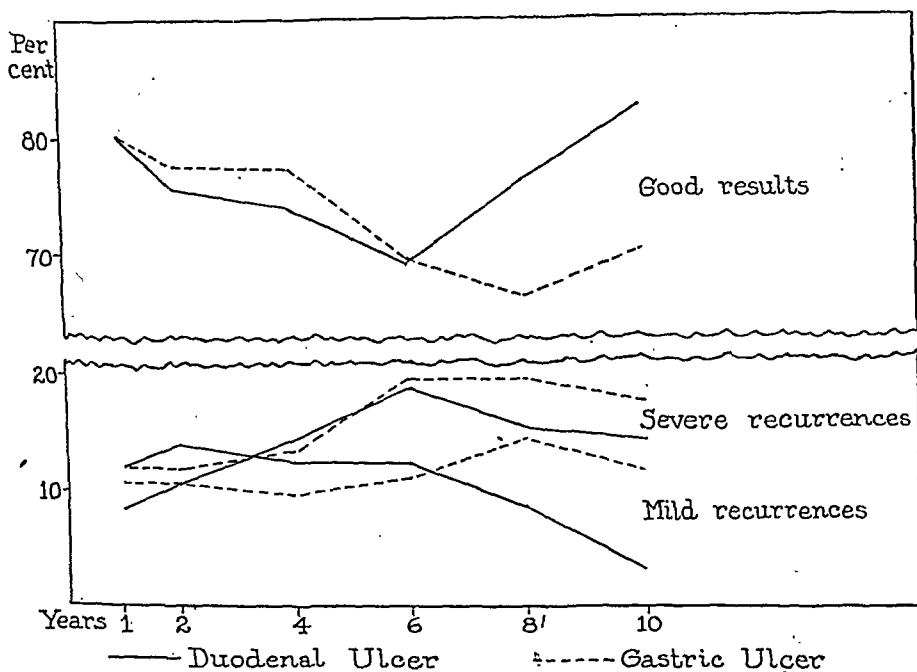


FIG. 1.—The late results of the surgical treatment of ulcer; a graphic representation of data published by Fremont-Smith and McIver.

**Gastric Ulcer.** The clinical pictures of gastric and duodenal ulcer are so similar that when a patient comes with the story of "hunger pain" returning in attacks once or twice a year, the expert does not attempt to say whether the lesion is above or below the pylorus. As a betting proposition he knows that the odds are about 8 to 1 in favor of its being below, but he makes no decision until he hears from the roentgenologist.

But if the diseases are so indistinguishable why worry about a difference of only a few centimeters in the location of the lesion? Because, if the ulcer is in the duodenum the fear of cancer can practically be dismissed; while if it is in the stomach the possibility of malignant degeneration must ever be kept in mind. I make this statement unequivocally and I am going to emphasize it in spite

of the fact that some gastroenterologists will still disagree with me. In 1923, when Jones sent a questionnaire to the members of the American Gastroenterological Association asking them how often they had seen a cancer develop in a gastric ulcer, some said they had never seen it, others thought it occurred in from 1 to 5 per cent and most of them thought the danger was so small as to be almost negligible.

Now, whenever two groups of reputable men of science disagree it generally appears later that both were partly right and both partly wrong, and usually because neither paid careful attention to see exactly what the other was talking about. One has only to look over the statistical reports on which many of the statements in the literature are based to see that little or no care was taken by the compilers to discriminate between duodenal and gastric ulcer. Obviously in such groups, made up principally of patients with duodenal ulcer, one would expect to find but few cases of cancer of the stomach, and the fact that physicians still continue to base their arguments on such statistics only shows how completely they have failed to comprehend the nature of the problem. Others fail to see or refuse to see that the big danger is not that an old ulcer will some day become cancerous but that the patient who has just come in with what looks like an ulcer is already suffering with cancer. We can as yet only speculate as to the number of old ulcers that become cancerous but we know that at The Mayo Clinic in 1926 one out of every seven gastric lesions that looked roentgenologically like an ordinary ulcer was found at operation to be malignant. Furthermore, for every four or five typical gastric ulcers seen by the roentgenologist there was an additional indeterminate lesion, and at operation half of these proved to be carcinomatous.

Some three years ago when I moved to Rochester I became much interested in the controversy over the origin of gastric cancer and more and more desirous of examining the data and of forming an opinion for myself. At first sight it might seem that a man who for eighteen years had been seeing a large number of patients with indigestion should have had an opinion, but after a little study I found why I had none.

The difficulty is that gastric ulcer is a comparatively rare disease. In 1926, at the Clinic, with a registration of 71,675, the roentgenologists examined 15,000 who complained of indigestion and diagnosed gastric ulcer in 225 and multiple gastric and duodenal ulcer in 47. One hundred and ten of these (1 in 650 registrations) were operated on and the ulcers removed and made available for microscopic study. Only 11 of these lesions were more than 2 cm. in diameter and, as will be brought out later, these were the ones which were most likely to be cancerous. During the same period the roentgenologists diagnosed cancer of the stomach in 375 patients and found indeterminate lesions in 47 more. A little more than half of these

patients were operated on and 24 of the lesions removed were found to be less than 3 cm. in diameter.

There were, therefore, during the year, 35 cases in which the pathologist had to be particularly careful in distinguishing between a benign and a carcinomatous ulcer. This represents an incidence of one in 2050 registrations. If a similar ratio holds in private practice then a physician who studies let us say 700 new patients a year and who has half of those presenting gastric lesions operated on by surgeons competent to do a resection will see one of these borderline lesions every three years. Under such circumstances he can hardly recognize the problem, much less form an opinion about it. We, on the other hand, who see one of these cases every ten days become greatly interested in them and become convinced of the great need for handling them properly.

But some may say, "Why bother about these cases if they are so rare?" The answer is that all cancers of the stomach must some time have a beginning and when they begin they almost certainly must be small. But where will we find some to study? Obviously, as they rarely cause death until they have extended widely we must find them accidentally at necropsies and at operations on the stomach. And what do they look like then? Very rarely a little adenomatous plaque is found; less rarely a polyp with malignant changes at some point, and commonly—and this is the important point—cancer is found in the walls of what looks like a large benign ulcer. It would seem obvious, then, that the only way in which we can every hope to get at early cancer of the stomach is to excise gastric ulcers.

These views are not based on observations made only at The Mayo Clinic. Wilensky and Thalhimer who made a careful study of 48 ulcerlike lesions classified 7 as carcinomas. One more was an ulcer with carcinomatous changes here and there along the edges and one was an apparently benign ulcer with the adjacent lymph glands full of cancer. Such cases have been seen several times by MacCarty.

In 1000 stomachs studied at necropsy, Cleland found cancer in 36. In 5, the lesion was small and was discovered only accidentally. One was a small papillomatous mass with malignant degeneration, one was a polyp with a malignant ulcer at the base and 3 were ulcers with carcinomatous changes in the wall. Although this change could be detected only microscopically, in 2 it was associated with widespread metastasis. Incidentally, the fact that this early dissemination of metastases is noted with a third of the small carcinomatous ulcers removed at The Mayo Clinic should somewhat silence those who still hold that our pathologists are mistaken as to the nature of the cell changes in the lesion itself. Apparently, then, in a series of 36 cancers of the stomach found at necropsy, 1 in 7 was unexpected and 1 in 12 was in the wall of an ulcer.

Stewart at Leeds studied 134 chronic gastric ulcers, 14 cancers apparently arising in chronic ulcers, and 68 cancers in which he could find no sign of ulcer. All were removed at operations. He concluded that 9.5 per cent of the chronic ulcers had become cancerous or 17 per cent of the cancers had originated in ulcers. Moynihan, with his great experience, believes that one cannot neglect the danger of cancerous degeneration in gastric ulcers. He expresses himself as feeling "acutely anxious as to the destiny of any patient suffering from gastric ulcer."

That the problem is a big one and that conditions cry out for improvement was shown in a recent paper by McVicar and Daly. They found that at The Mayo Clinic, in the five years from 1920 to 1924 inclusive, 2078 patients were seen with carcinoma of the stomach. Of these, one-half had to be sent home immediately as hopeless; the other half were operated on, but again, in only half could any attempt be made to remove the tumor. Three-fourths, then, of the cancers of the stomach which we now see are so large that nothing can be done about them.

The next question is: Who is to blame? In many cases no one is because the patient, with hardly a symptom, does not suspect his danger until the disease is far advanced; in others, members of our profession are to blame because for weeks and months they tried out one remedy after another for what they thought was transient indigestion or benign ulcer.

As I have already pointed out, many gastroenterologists today still have the idea that when we at The Mayo Clinic ask a patient with gastric ulcer to be operated on it is because we are afraid the lesion will later become cancerous. Although we do see many cases in which the history strongly suggests that this is a contingency to be feared, we are really more concerned with the possibility that the lesion before us, which looks like an ulcer, may already be malignant.

Often, of course, when we are dealing with a fairly young patient with a history running back several years, with normal amounts of hydrochloric acid, and a very small ulcer, we know that the odds are strongly in favor of its being benign. But this does not entirely satisfy us because with the large numbers of patients constantly going through our hands not a month passes that some one does not appear to startle us and sober us by breaking all the rules of statistical expectation.

Some physicians depend a good deal on the age of the patient but Fig. 2 shows that when it comes to making a diagnosis, the differences between the age distributions of patients with gastric ulcer and gastric cancer are too small to be of service. No one of us would care to risk his life on a "two to one shot."

With the training that we physicians had at college, it is hard for us to think of a ruddy, robust and perhaps slightly overweight man of forty years as having cancer of the stomach, and yet obviously

cancer must at some time in its course be so small as not to produce any symptoms, and certainly not such severe ones as emaciation and anemia. For years my associates at the Clinic have been trying to get physicians to see that our textbook pictures of carcinoma of the stomach, the pictures which we present to our medical students, are highly inadequate and misleading. We perhaps ought even to hide them because they are the pictures of cancer in its final and usually hopeless stage.

What we should be hammering home is the conception that early cancer must be looked for in normal, healthy looking men and women with only a slight deformity in the outline of the barium-filled stomach. Until this idea can be incorporated into that mass of medical impressions upon which all of us, physicians and laymen

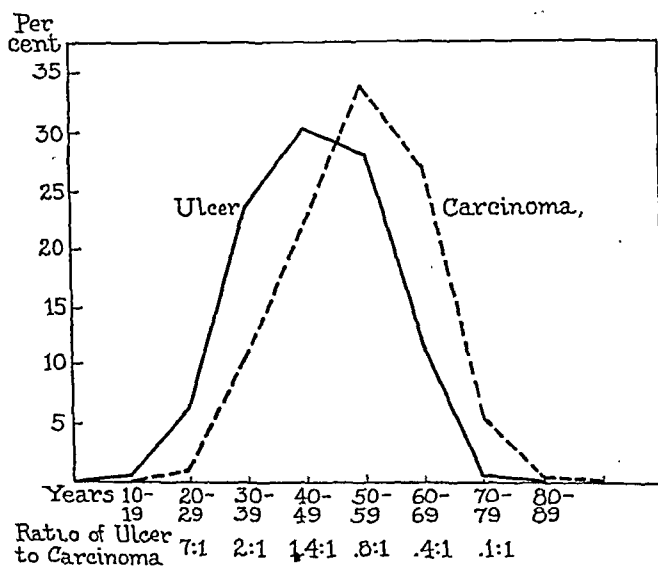


FIG. 2.—Percentage distributions showing the ages of 500 patients with gastric ulcer and 2086 patients with cancer of the stomach. The figures on the lowest line indicate the relative numbers of ulcer and cancer bearing patients at different ages.

alike, base our actions there is little use in talking about the early diagnosis of cancer of the stomach.

The objection may, of course, be raised and it is being raised, that the early carcinomatous changes seen by the pathologists at The Mayo Clinic may be but figments of their imagination. In order to satisfy my mind on this point I some time ago took advantage of Dr. MacCarty's kind offer to go over with him the hundreds of records collected in his laboratory in the last eight years. To simplify the problem I put aside the records of small ulcers and large cancers about which there can be little or no question and concentrated my attention on ulcers larger than 3 cm. in diameter and carcinomas smaller than 4 cm. in diameter. I did this because it seemed to me so obvious that if mistakes had been made, almost



all of them would be found in this borderline group of the largest ulcers and the smallest cancers.

With the help of Dr. Balfour's follow-up service I next looked up the subsequent history of the 126 patients from whom these possibly questionable lesions had been removed. Of the 15 with ulcers smaller than a half dollar (799 sq. mm.) all but one (who was a syphilitic) were in fair or good health when last heard from. Of the 8 with supposedly benign ulcers larger than a half dollar, 5 had died with what was either probably or certainly cancer of the stomach. Evidently then ulcers larger than a half dollar are almost always cancerous and our pathologists are not yet quite radical enough in recognizing early malignant changes.

The records of only 68 of the patients with "cancer" could be used in this study, the others having been operated on too recently for me to tell much from their subsequent course. Of the 68, 3 returned with general carcinomatosis; 16 were said by home physicians to have died of cancer, 2 died with symptoms suggesting recurrence, and 15 more were reported simply to have died. They too probably died of cancer because their demise came within that period of a year and a half after operation in which recurrences commonly kill. Over half, then of these persons who would seem from the unusually small size of the cancer to have had a good chance for life died shortly after the operation.

I will not go into all the details of the study but suffice it to say that when I was done I felt perfectly satisfied that there is nothing make-believe about the cancer now being diagnosed by our pathologists. When they say that an ulcer is benign the patient usually lives and when they say it is malignant the patient has only the usual fifty-fifty chance of living that he has after any good operation for early cancer.

As I have already said, we at The Mayo Clinic, even at the time of operation, know of no way of telling, except by examination of microscopic sections, whether an ulcer is or is not cancerous. Large lesions and especially lesions that produce filling defects are almost certainly malignant and with them a good roentgenologist seldom misses the correct diagnosis. But, as even Cole with his careful technique has admitted, when a lesion is first seen, "in approximately 10 per cent of cases it is difficult or impossible to state definitely from the radiologic evidence alone whether the case is one of simple ulcer or of cancer." This being true, where is one to get help in the diagnosis?

There is one point brought out in the history which is often very helpful in making a tentative diagnosis and that is the duration of the symptoms. Some time ago I examined 100 records of patients with benign gastric ulcer, proved by excision and microscopic section, and 100 records of patients with inoperable cancer of the stomach surgically explored. In Table II I have classified these histories

not only according to the duration of symptoms but also according to my opinion of the type of the history; that is, whether it suggested to me the presence of ulcer, of cancer, or of gall-bladder disease. Some of the stories were fairly typical for ulcer and others could only be called vague.

TABLE II.—THE LENGTH AND TYPE OF HISTORY OF INDIGESTION.

100 patients with gastric ulcer operated on at The Mayo Clinic in 1925, 1926, and 1927.		100 patients with inoper- able carcinomas of the stomach explored at The Mayo Clinic in 1926.	
Mos. Yrs.		Totals.	Totals.
1	g	1	4
2	vv	2	6
3			8
4	uvv	3	6
5	v	1	7
6	c	1	11
7			3
8	u	1	3
9			1
10	u	1	2
11			1
1	ug	2	15
2	uuu, a-u, vcc	7	12
3	uuuffv	6	4
4	uuf	3	1
5	uuuvffff	8	1
6-9	uuuuuuuuuuuuuvvvvvvffg	23	2
10-14	uuuuuuvvvff	12	7
15-19	uuuuuuvf	9	2
20-24	uuuuuf	7	2
25-29	uuuuf	5	2
30-34	uu, u-g, v	4	
35-39	g	1	
40	uvv	3	
		100	100

ABBREVIATIONS: u represents ulcer; v, vague; f, fair ulcer; c, carcinoma; g, gall-bladder disease; a, appendicitis; obstr., obstruction.  
Each letter or combination of letters represents a case.

It will be seen at a glance that a few of the patients with gastric ulcer came to the Clinic in the first or even the second year of the disease. Most of them had had symptoms for from five to thirty years. On the other hand, 79 of the 100 with cancer of the stomach had had symptoms for less than two years (Fig. 3).

No matter, then, what one thinks about the etiologic relationships of ulcer and cancer there is no getting away from the fact that it is very dangerous to treat medically any patient with a gastric lesion and a short history. Many physicians say, "Well and good, we admit that, but why not treat such a patient medically: if he improves and gains in weight we can stop worrying; if he does not respond properly we can call in a surgeon." This plan sounds reasonable but in practice it often fails, and not a month passes at

the Clinic that we do not see an example of the type of disaster that can result from placing reliance in it. The trouble is that although the cancerous lesion often fails to respond to ulcer management it does not always do so. Sometimes it responds beautifully; symptoms disappear, the patient gains in weight and everyone for a time is delighted. Later, when the collapse comes, metastatic nodules are everywhere and it is too late to do anything.

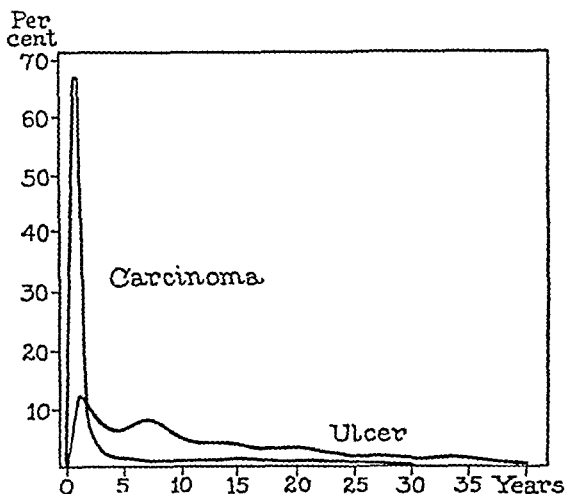


FIG. 3.—Percentage distributions showing the marked difference in the duration of symptoms in patients with ulcer and cancer of the stomach.

Doubtless there will always be cases of gastric ulcer which for one reason or another will have to be treated medically, and obviously, the most suitable subjects for such treatment will be the younger patients with a history of several attacks, a small ulcer, and perhaps normal gastric acids. But even in these cases, with the chances largely in favor of the lesion being benign, the conscientious physician will remain uneasy and will insist on watching the ulcer with the roentgenoscope until it either disappears or begins to grow larger.

I say this in spite of the fact, emphasized by many clinicians throughout the world, that there are many patients with gastric ulcer who can be treated medically for years without the appearance of cancer. A glance at Table II shows that this must be so, otherwise 19 out of 100 persons with gastric ulcer could not have lived as they did to tell a story of typical attacks of pain running back fifteen, twenty, thirty and even forty years. If we include 9 with fair or vague ulcer stories we have 28 out of 100 with symptoms for more than fifteen years.

Table II and Fig. 3 show also that patients with cancer of the stomach rarely admit having been ill for longer than two years, and that in only about 16 per cent does routine questioning bring out a story of symptoms suggesting ulcer running back more than

two years. Believing as I do that cancer commonly develops on the basis of ulcer, I am forced to the conclusion that ulcers which become cancerous are either of the symptomless variety or else the persons who bear them are peculiar; that is, they are so prone to malignant degeneration that the changes take place as soon as there is any break in the mucosa of the stomach.

A patient illustrating such a marked tendency to cancer formation was recently shown me by Dr. Bargaen. The man came to the Clinic in 1922 with two distinct cancers in different parts of the colon. They were resected and five years later he returned with two more distinct cancers of the colon. One brother had died of cancer of the colon and another is now being treated at the clinic for the same disease. Probably Maude Slye is right and some of us are immune to cancer and others highly susceptible.

Somewhat against my theory is the fact that I have already found a few patients with old benign ulcers who now have cancer in the colon or prostate, but it must be remembered that in many persons, as in Miss Slye's mice, cancer susceptibility and immunity may be limited to certain organs or tissues. Another big objection to the ulcer-cancer theory is the fact noted in Table II that in only 2 out of the 67 cancer-bearing patients with symptoms for a year or less did the story sound to me like that of definite ulcer. Other clinicians might disagree with me but that was my impression obtained from the particular histories studied.

Of one thing I can be sure and that is that any form of indigestion or constipation, no matter how mild or vague, which comes out of a clear sky after the age of forty years, must be investigated immediately and thoroughly and with the help of a really expert roentgenologist. Certainly no applicant for insurance with such a story should be accepted until it is certain that the outlines of stomach and colon are normal, and even then he will bear watching.

One big reason why we should all be making an effort to estimate more exactly the danger of malignant degeneration in old chronic gastric ulcers is that the bearer of such a lesion cannot flee from this vaguely outlined menace without running into the very real danger of death from subtotal resection of the stomach. Under the circumstances, any patient who is at all inclined to reason statistically will want to know the probabilities; that is, he will want to balance the mortality rate for cancer against the mortality rate of the particular surgeon who is to operate on him. Seeing that physicians are daily being called on to help in making this decision, it is a shame that as yet, they have not at their command the information which they need.

The only "proof of the pudding" in insurance work comes through obtaining data on actual experience with a sufficient number of risks. Actually Balfour and Hunter showed in 1919 that after operations for gastric ulcer the mortality was higher than normal.

There were 521 patients observed for an average period of 3.6 years. The immediate surgical mortality was 4.5 per cent. During the period of observation 17 per cent died, while in the group of 1651 patients operated on for duodenal ulcer only 5 per cent died. Most of the excess mortality in the cases of gastric ulcer came in the first three years when carcinoma, missed at the operation, may have been taking its toll.

That actuaries still need more definite information is indicated by a paper published by Morgan in 1926. He wrote to eighteen representative companies to ask what their practice was in regard to applicants with a history of duodenal ulcer. Seven refused all with a history of gastric ulcer; seven accepted applicants with duodenal ulcer if free from symptoms for two years after surgical treatment or for five years after medical treatment, and two made the same ruling in regard to patients with gastric ulcer. Seven refused all applicants with duodenal ulcer not operated on and nine refused those with gastric ulcer not operated on.

**Conclusions.** Scars of peptic ulcer were found more or less unexpectedly during 3.4 per cent of 2000 necropsies performed at The Mayo Clinic, and open ulcers were found more or less unexpectedly in 7.4 per cent. Ulcers are diagnosed roentgenologically in about 3.3 per cent of the patients who register at the Clinic or in 15.5 per cent of those who complain of indigestion.

Women with ulcer often suffer also from gall bladder disease and they often submit to appendectomy and to operations on the pelvic organs.

Peptic ulcer is a serious disease based on some predisposition which in many persons causes the lesions to reappear again and again even after excision of part of the stomach.

In the early stages of the disease it is, in most instances, easy to relieve symptoms but in more than half of the cases they tend to recur.

The danger of death from bleeding or perforation is small.

Many of the patients with chronic ulcers must eventually be operated on and that carries a risk. For the first few years after operation the results are generally good but as years pass, an increasing number of the patients relapse; from 5 to 10 per cent have to be operated on again, and many become more or less incapacitated.

For this reason, persons with ulcer are not fit subjects for health insurance. Great care must be taken to distinguish between those with duodenal and gastric ulcer not only on account of the higher risk of operations for gastric ulcer but because there is a definite possibility either that the lesion is cancerous at the time of examination or that it will become cancerous later.

Persons past forty years with recently acquired indigestion of any kind are particularly undesirable as risks. It is impossible in many cases to distinguish, even at operation, between benign and malignant ulceration.

The only way in which to cure cancer of the stomach is to operate on healthy looking men and women with a slight but definite irregularity in the outline of the barium filled stomach.

Persons with duodenal ulcer might be accepted as substandard risks when, after either medical or surgical treatment, symptoms have been absent for six years.

Only long experience can give exact information as to what premiums patients with gastric ulcer should pay for insurance. From the statistics presented, it would seem obvious that no one over thirty years of age should ever be accepted when the symptoms have been of short duration and when a "cure" has been but recently accomplished.

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## CHRONIC DUODENAL STASIS OBSERVATIONS IN TWENTY-FOUR CASES.\*

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ALTHOUGH chronic dilatation of the duodenum has long been recognized, it is only within recent years, that any actual clinical significance has been attached to this affection. Aside from congenital factors, the following conditions favor its formation; adhesions, compression of the duodenum and prolapse of the colon into the pelvis. Adhesions ordinarily involve the first and second portions of the duodenum. Especially important in this direction are the obstructions produced as the result of adhesive processes due to intraduodenal lesions, as ulcer or tumor; chronic cholecystitis; adhesions between the duodenum and hepatic flexure and those formed as the result of visceroptosis or following abdominal operative procedures. Pressure on the duodenum occasioning duodenal stenosis may result from spinal deformities and also from growths involving abdominal organs such as the pancreas and from pressure

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due to ptosis of the right kidney. It is of importance to note, however, that according to Bloom and Arens as well as others, that inasmuch as chronic duodenal stasis is observed so frequently intimately associated with other affections, it should not be considered as a distinct clinical entity, but only as a radiologic phenomenon the result of such lesions. This view has not been accepted by most authorities.

**Incidence.** Chronic duodenal stenosis may occur at any age. The youngest case reported is that of three years, the oldest of sixty-six years. The highest incidence of this affection occurs during middle life, that is between thirty and forty years.

Of the 24 cases of chronic duodenal stasis in our series, 18 were males and 6 females. It is maintained by most authorities that this affection occurs twice as frequently in females as males which is contrary to the findings in our cases.

TABLE I.—CASES ARRANGED ACCORDING TO AGE AND SEX.

Age (years).	Males.	Females.
20 to 30 . . . . .	2	1
30 to 40 . . . . .	10	4
40 to 50 . . . . .	4	1
50 to 60 . . . . .	2	0
Total . . . . .	18	6

**Symptomatology.** The symptoms of chronic duodenal stasis, according to our experience, are not always characteristic, especially in mild forms. In these cases, there are often periodic attacks of nausea and vomiting so-called bilious attacks which may have occurred over a period of many years, often since childhood. These are frequently preceded by intense constipation and are often accompanied with headaches and migraine attacks. The constipation is occasionally replaced by intermittent outbreaks of diarrhea. Attacks of nausea and vomiting occurred in 18 of our cases; migraine attacks in 15; constipation in 19; intermittent diarrhea in 3. Pain may be absent, mild or severe and may present no special relation to food. This symptom occurred in 16 of our cases; in 9 of which it was mild and in 7 severe. Changes in posture may in some instances afford relief from this symptom. Occasionally, the liver enlarges with an attack and tenderness may occur at this time under the right costal arch. Tenderness under the right costal arch with enlargement of the liver was noted in 5 of our cases. Due to the frequency of these attacks, loss of weight and strength is not unusual and neurasthenic symptoms are apt to supervene. During the interval of freedom from these attacks which may extend over a period of some days, the patient may enjoy comparatively good health. While in the milder intermittent type associated with infrequent attacks the pylorus retains its normal tonicity and



regurgitation takes place only when the obstruction permits an excessive amount of duodenal contents to accumulate. In the more chronic and severe forms, the pylorus becomes patent and dilatation of the stomach may occur. In many of these cases the pylorus remains constantly open and is greatly increased in diameter, often to such a degree that nausea and vomiting of bilious contents becomes more or less persistent and even vomiting of the retention type may occur, as was noted in 2 of our cases. The patient may complain of fullness, heaviness and distention and of eructations of gas following meals and not infrequently of pain which may extend over the entire abdomen or be limited to the epigastrium, or right upper or lower quadrants of the abdomen. Headaches become incessant and migraine attacks with bilious vomiting, malaise, faintness and dragging sensations are not infrequent. Occasionally an urticarial eruption is observed; this occurred in one of our cases. The symptoms vary somewhat according to the location of the obstruction. When obstruction occurs at the first part of the duodenum, the symptoms largely resemble those of pyloric stenosis. In other instances, pain extending over the gall-bladder region with enlargement of the liver and jaundice may erroneously give rise to the diagnosis of cholecystitis. This error occurred in 2 of our cases. In still others, pain may occur several hours following meals together with symptoms of hyperacidity and consequently an incorrect diagnosis of ulcer may be made, as was noted in 3 of our cases. Occasionally the attacks may disappear for periods of months or even years during which the patient may enjoy good health, when a relapse may occur following an acute illness, such as grippe. The discomfort and pain which is usually present in these cases during an attack and which is frequently aggravated in the recumbent posture may be relieved at times by elevating the pelvis or having the patient assume the knee-chest posture. These procedures were of distinct advantage in overcoming attacks in many of our cases. In the very aggravated types with gastric retention and profuse bilious vomiting a high degree of toxemia may occur. This may be associated with marked dehydration, shock and at times with attacks of tetany.

Among the associated conditions noted, peptic ulcer is most important. Gastric ulcer occurred in three of our cases; an esophageal diverticulum in one, mucous colitis in three and cholecystitis in one.

**Case History.** The following history presents the most important features of a typical case. D. B. F., male, aged forty-three years, had been complaining of indigestion for many years, consisting of attacks of pain in the upper right quadrant, with discomfort in that region running into the back toward the right shoulder blade. In the spring of 1909 these attacks became more severe and frequent, and the diagnosis of cholecystitis was made and a cholecystostomy was performed. No stones were found but the diagnosis of chronic cholecystitis was confirmed.

The patient remained well for a number of years but within the last two or three years had frequent attacks of nausea and vomiting. The vomitus recently contained food ingested several days previous. With this, there has been considerable discomfort in the upper right quadrant; headaches; fullness and distention after eating and gaseous eructations. The patient, in consequence, has been forced to live on a restricted diet. He is very constipated and has lost about 10 pounds in weight.

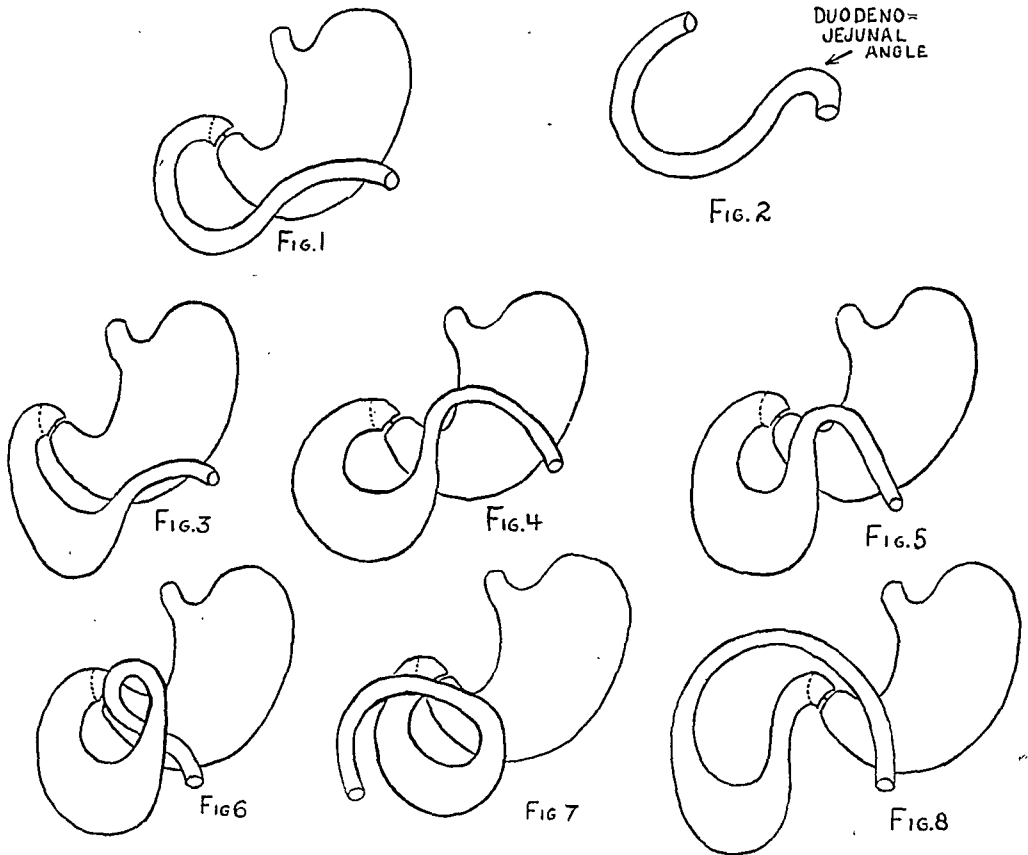


FIG. 1.—Schematic drawings; Fig. 1 illustrates the normal duodenal curve with relation to stomach; Fig. 2, normal duodenal curve. Fig. 3, shows a sagging of the duodenum with normal duodenal curve. Figs. 4, 5, 6, 7, 8, shows a sagging of the duodenum, with interference of the normal duodenal curve, resulting in stasis.

On examination, the chest organs were found normal. The abdomen was slightly distended, but there were no enlargements, masses, or peristaltic waves present and there was distinct tenderness under the right costal arch. The test meal showed a total acidity of 18 with the absence of free hydrochloric acid but contained considerable mucus. A meal given at night and extracted the following morning, disclosed considerable retention. The Roentgen ray examination was as follows: The position of the stomach is normal. There are no filling defects present. The duodenal cap is dilated but regular in outline. The second portion is markedly dilated, showing a distinct retention and constriction at its distal portion. A sacculum, about the size of a dime is also observed, projecting from the inner aspect of the second portion of the duodenum, which suggests the ampulla of Vater. The colon is in normal position. The diagnosis of the duodenal stasis with definite retention was made, which was confirmed by subsequent examinations.

TABLE II.—IMPORTANT FINDINGS OF 24 CASES OF DUODENAL STASIS.

Name.	Sex.	Age.	Pain.	Migrainous attacks.	Nausea and vomiting.	Constipation.	Diarrhea, intermittent.	Enlargement of liver with tenderness.	Associated conditions.	Dilatation of second portion of duodenum.	Röntgen ray findings.
1. H. V. U.	M	41	+	+	+	+	0	0	Ulcer	...	Duodenal cup dilated, stasis in second portion of duodenum, pyloric ulcer.
2. S. D. F.	M	59	0	0	0	0	0	0	Mucous colitis	...	Slight duodenal stasis, second portion.
3. H. P. N.	M	34	+	+	+	+	0	0	Mucous colitis	...	Adhesions.
4. H. F. W.	M	29	+	+	+	+	0	0	Mucous colitis	...	Adhesions.
5. E. C. L.	M	39	+	+	+	+	0	0	...	+	Adhesions.
6. B. S.	M	43	+	+	+	+	0	0	Cholecystitis	...	Duodenal stasis; gastric retention, second portion of duodenum irregular.
7. S. L. P.	M	36	+	+	+	+	0	0	...	...	Duodenal stasis, second portion.
8. T. B.	M	56	+	+	+	+	0	0	Esoph. divertic.	...	Marked dilatation of duodenal cap, with slight gastric retention, result of extensive right upper quadrant adhesions.
9. D. H.	F	38	0	+	+	+	+	+	Jaundice	...	Constriction in upper jejunum, resulting in duodenal stasis.
10. A. H. W.	M	37	+	+	+	+	0	0	...	...	Constriction in third portion of duodenum with dilatation and dilated duodenal cap.
11. L. A.	M	37	+	+	+	+	0	0	Mucous colitis	...	Slight stasis in second portion of duodenum.
12. A. D. M.	M	32	0	+	+	+	0	0	Jaundice	...	Dilated duodenal cup, duodenal stasis with marked angulation of third portion.
13. R. J. S.	M	35	+	+	+	+	0	0	...	...	Duodenal stasis.
14. S. R.	F	32	+	+	+	+	0	0	...	...	Marked angulation of duodenum with duodenal stasis.
15. T. G. O.	M	31	+	+	+	+	0	0	...	...	Marked angulation of duodenum with stasis in second portion.
16. B. J. T.	M	37	+	+	+	+	0	0	...	...	Gastric retention.
17. B. C. H.	M	46	+	+	+	+	0	0	...	...	Stasis in second portion.
18. T. H. L.	F	26	+	+	+	+	0	0	...	...	Stasis in second portion.
19. M. O.	F	43	+	+	+	+	0	0	Pyloric ulcer	...	Stasis in second portion.
20. D. B. F.	M	34	+	+	+	+	0	0	Gastric ulcer	...	Stasis in second portion.
21. M. T. A.	M	26	+	+	+	+	0	0	...	...	Stasis in second portion.
22. O. F. L.	M	47	+	+	+	+	0	0	...	...	Stasis in second portion.
23. G. F. L.	M	33	+	+	+	+	0	0	...	...	Stasis in second portion.
24. S. H.	F	...	...	...	...	...	...	...	...	...	Stasis in second portion.

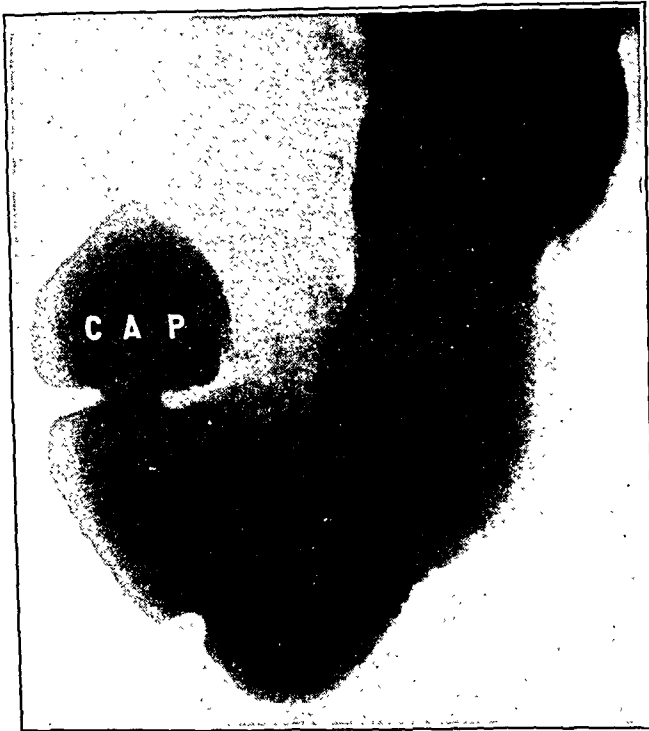


FIG. 2.—Shows a dilated duodenal cap forty-five minutes after a barium meal. No barium observed beyond the cap.

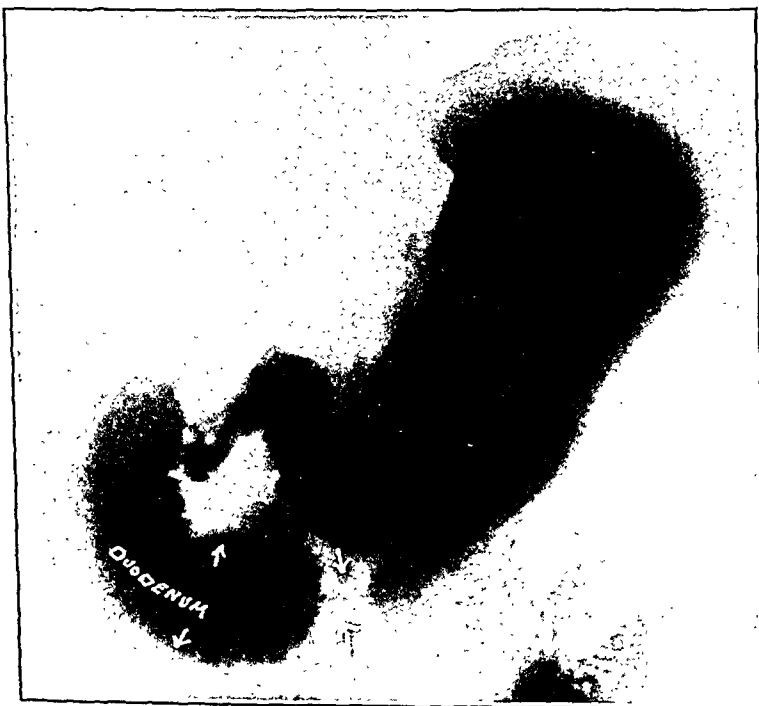


FIG. 3.—Dilated descending and transverse portions of the duodenum, with a constriction at junction with ascending portion.

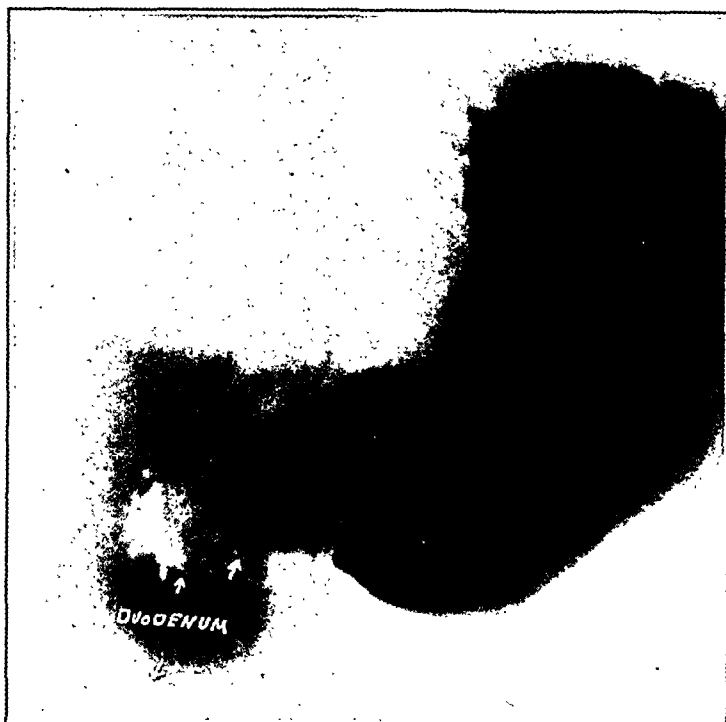


FIG. 4.—Lagging of barium in transverse portion of duodenum forty-five minutes after a barium meal; no barium observed beyond this portion.

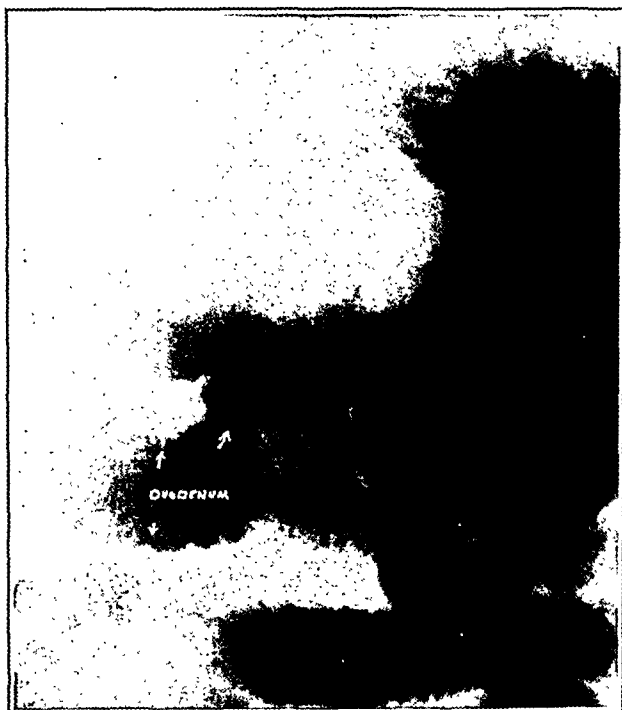


FIG. 5.—Lagging of barium in transverse portion of duodenum; the meal continues to pass on into the small bowel.



FIG. 6.—Constriction in jejunum, causing stasis; no barium beyond constricted area after one hour.

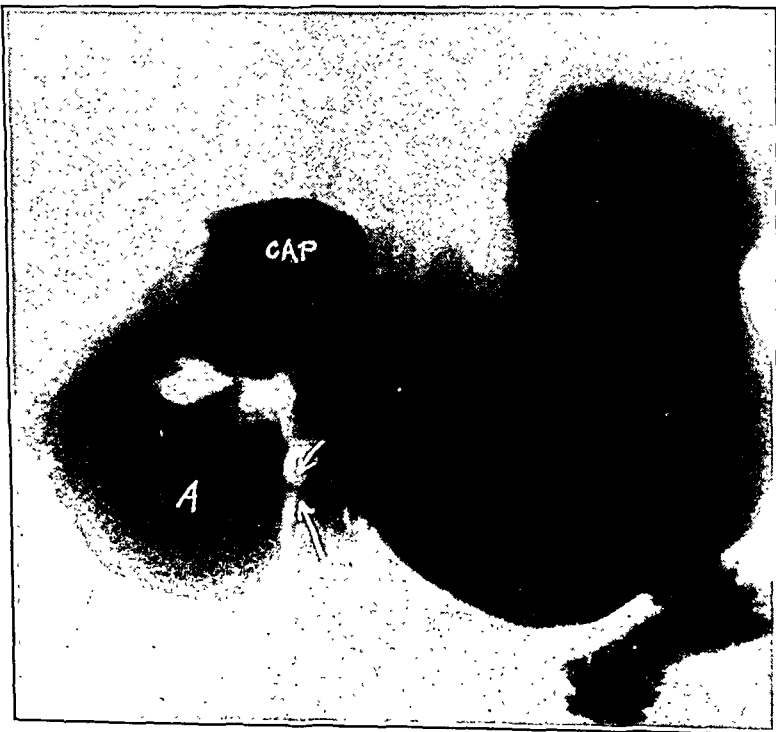


FIG. 7.—Illustrates marked dilatation of duodenum, resulting in partial obstruction; arrows point to constriction.



**Diagnosis.** The patient is usually observed to be slender of the asthenic type, presenting the narrow costal angle usually observed in visceroptosis. The stomach and colon are prolapsed and atonic and a succussion sound is readily elicited over the gastric area. Tenderness is ordinarily noted in the epigastrium or to the right or left of the umbilicus and an epigastric protuberance is occasionally observed. At times there is a general abdominal distention and the duodenal dilatation may be so marked as to present the sensation of a tumor mass to the palpating hand. This mass may be tympanitic or a succussion sound may be elicited from it and pressure over it may produce nausea.

In the milder type the gastric acidity is usually normal. Occasionally hypochlorhydria or hyperchlorhydria may occur. In the more severe forms, due to the admixture of large quantities of bile, achylia is usually present. The gastric contents may present all of the characteristics observed in pyloric stenosis, containing remains of food ingested on the previous day together with an admixture of dark-green bile and much mucus.

Of our 24 cases, the gastric acidity was normal in 13 instances; hyperchlorhydria was present in 7 instances and hypochlorhydria and achylia in 4.

While the diagnosis is made possible in rare instances from the history and physical findings alone, the Roentgen ray evidence is far more conclusive. The Roentgen ray signs of this affection are well defined and extremely characteristic and a certain diagnosis can only be made by means of this procedure. The Roentgen ray findings are based largely upon fluoroscopic examinations by means of which changes in motility can be carefully observed. The films, however, record the definite anatomic changes. The fluoroscopic examination is usually most satisfactorily made with the patient in the upright posture when viewed semilaterally with the right side nearest the screen. However, the obstruction can ordinarily also be well observed when the patient is recumbent and satisfactory films may be obtained in either position. Delay in the barium meal is not infrequently overcome by change in posture of the patient which can readily be observed under the screen. When an accumulation of barium occurs in the duodenum at any point, the mass is divided and passes in opposite directions along this organ. Retention in the duodenum can be considered positive when the barium is retained longer than a period necessary to complete the passage of two gastric peristaltic waves. In the more marked cases, however, gastric as well as duodenal six-hour residues of the barium are not uncommon.

The dilated duodenum can frequently be most satisfactorily observed from one to two hours following the barium meal. At times evidence of antiperistalsis with regurgitation of the barium meal into the stomach are noted fluoroscopically. In order to



eliminate the presence of duodenal stasis, the duodenum must be observed at intervals over a period of at least thirty to forty minutes. The presence of this condition is suggested when the duodenum is constantly visible during the period of emptying of the stomach.

In stenosis, between the first and second portions of the duodenum, the duodenal bulb may be elongated, dilated and will present evidence of delay in the expulsion of the barium. The first portion may also be distorted giving rise occasionally to the appearances noted in ulcer. In some instances, visualization of the third portion of the duodenum may be obscured, due to an enteroptosis, and lateral views must then also be obtained. The stomach is usually prolapsed in these instances, and may present a six-hour as well as an eighteen-hour retention. In these cases the barium passes without difficulty through the first part of the duodenum to the transverse portion where it remains stationary. At this point, violent peristaltic movements (the so-called writhing duodenum) are noted as if the barium were forcing its passage through some obstruction, when reverse peristalsis suddenly takes place and the barium is carried back into the duodenal bulb. These phases are rapidly repeated and after a certain delay portions of the barium are forced through the area of obstruction into the jejunum. Above the area of apparent obstruction dilatation of the duodenum is noted.

Obstruction of the second portion of the duodenum is usually more readily visualized. A rather characteristic picture is observed four to five hours following the barium meal in the form of a saucer-shaped residue in the second and third portions of the duodenum. The duodenum may be dislodged downward or it may present itself forward, being freely movable in the abdomen. Obstruction of the fourth portion of the duodenum is usually easily visualized. Stasis occurred in most of our cases in the second and third portion, the most frequent site being in the second portion. In one instance, it occurred in the upper jejunum, resulting in duodenal stasis.

Finally, in considering the diagnosis it should be recognized that duodenal stasis is not a rare condition and that it is not infrequently overlooked. In some instances, in fact, the affection may continue on for long periods without presenting symptoms. It is always important, however, in order to be certain that the stasis is permanent that repeated Roentgen ray examinations be made. Repeated examinations were made in all the cases in our series. Inasmuch as headaches associated with nausea and vomiting are frequently present, the diagnosis of migraine is not uncommonly made. It is, therefore, important in all obscure forms of migrainous headache that thorough roentgenologic studies of the duodenum be made. In some instances, the symptoms are attributed to gall-bladder disease, ulcer or even to neurasthenia.

As the clinical history of the affection is often indefinite, certain characteristics should be held in mind. Occasionally, there will be

single attacks following meals of but a few days duration, disappearing for a variable period of time and again recurring. At other times, the attacks may occur daily, following one or other of the meals. It is important to note that the attacks may have their onset in childhood and yet the condition not be recognized until later in life when the symptoms become sufficiently urgent to demand thorough investigation. In many instances the attacks appear suddenly following relaxation of the abdominal organs as after serious debilitating diseases or pregnancy, though even in these instances minor or fleeting attacks may have manifested themselves at times for long periods, the true nature of which may have remained unrecognized.

**Treatment.** In many instances, medical management is quite satisfactory and with conservative and postural treatment marked improvement frequently takes place. This is ordinarily observed in the milder types in which the symptoms occur intermittently and are followed by periods of relief. The cases due to visceroptosis are especially amenable to medical treatment.

Diet plays an important rôle in the management of these cases. This should be bland and of a high caloric value. Forced feeding and absolute rest in bed of from four to six weeks together with postural treatment is often indicated. Duodenal lavage through the Rehfuß tube is frequently of great benefit.

When the symptoms are severe or when adequate medical treatment no longer suffices in affording relief, surgical intervention is indicated; the most satisfactory procedure in most instances being duodenojejunostomy. When performing this operation, it is most important to undertake a complete investigation of the abdominal viscera, so that all complications may as far as possible be corrected during the time of this procedure. If the gall bladder is found diseased or when a peptic ulcer is detected or dilatation of the stomach exists, the procedures ordinarily undertaken for relief of these conditions should be carried out. When the duodenal stenosis is caused by adhesions, these should be released and if the duodenum is found markedly dilated and atonic a duodenojejunostomy should be performed.

The more radical measures, as extensive resections of the colon when coloptosis is present as a complicating factor, rarely warrant their extreme risk. Suspension of ptosed viscera is likewise ordinarily unsuccessful in its results.

Of our 24 cases on which this study is based, 23 were treated by means of the medical measures already referred to, with at least satisfactory temporary relief. In a single instance, which resisted this form of treatment, duodenojejunostomy was followed by complete recovery.

**Summary.** An analysis of 24 cases of chronic duodenal stasis leads to the following conclusions:

The condition is made possible both by anatomic and embryologic factors, and by conditions favoring adhesions or pressure on the duodenum due to spinal deformities or growths in the abdomen or traction on the mesentery due to visceroptosis.

In some instances, no demonstrable lesion has been ascertained; in the more chronic forms however, the pylorus is patent and there is permanent dilatation of the first three portions of the duodenum. Duodenal stenosis may occur at any age, though the greatest incidence is during middle life. According to most authorities, it occurs twice as frequently in females as in males.

The symptoms are not always characteristic, especially in the milder forms. There are periodic attacks of nausea and vomiting, so-called bilious attacks. There is often constipation with intermittent outbreaks of diarrhea. Change in posture may afford relief of symptoms. Loss of weight and strength is not unusual and neurasthenic manifestations are common. During the interval of freedom from attacks, the patient ordinarily enjoys good health. As the disease becomes more chronic the dilatation extends into the stomach, when nausea and vomiting become persistent. Headaches and migraine attacks are not infrequent. In the more aggravated types a high degree of toxemia may develop.

As associated conditions, a number of instances of peptic ulcer have been recorded. Gastric dilatation of varying degrees is not uncommon. Cholecystitis and pancreatitis occur due to an ascending infection.

In the diagnosis the presence of visceroptosis is important. The only conclusive evidence of this condition can be obtained by means of the Roentgen ray which reveals a delay or retention of the barium in the dilated duodenum.

In many instances, medical management is quite satisfactory especially in those instances due to visceroptosis. In the severe types accompanied by excessive vomiting and dehydration with a threatened alkalosis, the intravenous administration of sodium chloride solution with glucose is indicated. When the symptoms are severe or when adequate medical treatment no longer suffices in affording relief; surgical intervention is indicated, the most satisfactory procedure being duodenojejunostomy.

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## THE EFFECT OF INTRAVENOUS INJECTIONS OF VARIOUS EMULSIONS OF FAT ON THE EMPTYING OF THE GALL BLADDER.\*

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INVESTIGATORS in the field of gastrointestinal physiology are agreed that the ingestion of food rich in fat causes more or less complete evacuation of the gall bladder. Furthermore, there is

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general agreement in the conclusion that this evacuation, more extensive in certain species of animals than in others, is effected by the active contraction of an intrinsic musculature within the tunic of the gall bladder. This conclusion, which was reached independently by at least three groups of workers and supported by adequate experimental evidence, largely minimizes the earlier recorded observations that extrinsic factors, such as secretory pressure or intraabdominal pressure, were primary in their effect on the flow of bile from the gall bladder. Whitaker,<sup>12</sup> in commenting on the mechanism of the gall bladder, concluded that extrinsic factors do not have an appreciable influence, but that emptying of the vesicle is produced primarily by contraction of the muscle layer. He further concluded that contraction is probably not dependent on a reflex nervous mechanism, and that the evidence is not conclusive that hormone action is the exciting factor.

Egg yolk and cream, first used by Boyden<sup>1</sup> in experimental studies on the gall bladder, is perhaps the diet most effective in emptying the viscus. Since Boyden's significant observation, Whitaker has shown that emptying of the gall bladder could likewise be produced in cats by the ingestion of other fats. Subsequently, Krause and Whitaker<sup>9</sup> reported their observations on the gall bladders of cats following the ingestion of various food substances, such as olive oil, cod-liver oil, cocoanut oil, and certain carbohydrates, as well as protein substances. They concluded that fats and fatty acids are by far the most active in emptying the gall bladder, that carbohydrates are practically ineffective, and that pure proteins produce but slight emptying of the viscus.

Boyden<sup>2</sup> concluded that the gall bladder may be a trigger mechanism, set off by a number of foods, but that the degree or extent of emptying will depend on the time the digesting food is withheld in the stomach. Boyden and Saunders<sup>5</sup> further showed that when food is placed directly into the duodenum the extent of contraction of the gall bladder is not lessened. Higgins<sup>7</sup> observed that when food is introduced directly into the duodenum of a fish, sustained contraction of the gall bladder was not induced for periods ranging from an hour to an hour and a half. The initial stimulus of the food on the duodenal mucosa did not have any appreciable effect on the biliary vesicle, and it was not until considerable absorption had occurred and the residual food content had reached the lower intestines that the gall bladder contracted. In these observations on the fish, it must be recalled that laparotomy was done so that observations were made on the exposed viscera, a procedure which may or may not explain the prolonged interval between the feeding and the contraction of the viscus.

Fatty foods, however, are not the only substances that cause partial or complete evacuation of the gall bladder. Magnesium sulphate, when injected directly into the duodenum of man, causes

an expulsion of bile from the gall bladder induced by active contraction.<sup>5</sup> Subsequently, it has been shown that magnesium chlorid and sodium sulphate in strong solutions cause as effective a discharge of bile from the gall bladder of human beings as magnesium sulphate.<sup>4</sup> This is true whether these salts are administered by mouth or introduced by a Rehfuß tube. Although marked intestinal peristalsis has been induced in experimental animals by these salts, yet failure of the animal's gall bladder to contract casts considerable doubt on the validity of earlier observations that peristalsis of the gastrointestinal tract induces the organ to empty.

Besides these salts, certain acids have been shown to induce the flow of bile from the gall bladder. It has been known for a long time that a few drops of a weak solution of hydrochloric acid will cause bile to flow from the biliary duct system. Elman and McMaster<sup>6</sup> demonstrated that relaxation of the mechanism of the sphincter at the end of the common bile duct could be induced by a tenth-normal solution of hydrochloric acid. Boyden and Birch<sup>3</sup> were not able to secure as effective a discharge of bile from the common duct following lavage with hydrochloric acid as they did following the drinking of a glass of water. On the other hand, Ivy and Oldberg<sup>8</sup> were able to induce contraction of the gall bladder in animals by the introduction into the duodenum of 20 to 30 cc. of tenth-normal hydrochloric acid. Subsequently, these authors, from studies on cross-circulation experiments, concluded that hydrochloric acid given into the duodenum to one animal may induce the contraction of the gall bladder of the second animal within ten minutes. Some action of an hormonal nature incited within the duodenum of the first dog becomes effective by passage through the blood stream into the second animal.

In addition to the mechanism set up within the gall bladder either by nervous stimulation or by hormonal activity, a regulatory mechanism guards the portal of the common duct into the duodenum. The literature on the sphincter of Oddi, its physiology and anatomy, and its presence or absence, is enormous, and no attempt will be made to review it here. It is sufficient to state that the best authorities on the physiology of the extrahepatic biliary tract are rather agreed in affirming the existence of some regulatory mechanism at the duodenal end of the common bile duct which functions in a way to regulate largely the filling and emptying of the gall bladder.

**Method of Study.** Although the gall bladder is known to react to various saline cathartics, acids and even to mechanical disturbances, its essential physiologic rôle seems in some way correlated with metabolism of fat. Since we have observed the emptying of the gall bladder in animals in which the duodenum had been experimentally isolated from the gastrointestinal tract, we believe that at least the duodenal mucosa did not play an essential part in causing the con-

traction of the viscus. Sosman, Whitaker and Edson<sup>11</sup> had shown that in cases of pyloric resection and gastrojejunostomy the gall bladder emptied as well after eating as in the normal subject. It has seemed to us that the amount of bile discharged from the gall bladder has appeared to be in some way correlated with the absorption of fat. Krause and Whitaker<sup>9</sup> had observed in their study of the effect of various foods that "the degree of absorption of fat is probably related to the degree of the emptying of the gall bladder." Whether the degree of contraction of the vesicle is dependent on the extent of absorption cannot be stated. More than likely the gall bladder bile facilitates digestion, thus securing greater absorption. In a recent study of the relation of the emptying of the gall bladder to the digestion of fats, Silverman, Denis and Weinberger<sup>10</sup> concluded that such emptying is not dependent on the absorption of the fat, so far as can be determined by analysis of the blood for fat.

We were prompted to try a series of experiments in which various highly emulsified fats were injected directly into the blood stream. Whitaker<sup>12,13</sup> has described the intravenous use of an olive-oil emulsion which was followed by the emptying of the gall bladder. He also showed that an intravenous injection of liquid petrolatum was nearly as effective as olive oil in this respect. For some time one of us (Wilhelmj) has been conducting a series of observations on the metabolism of fats following both oral and intravenous administration. Since the slow intravenous injection of various fat emulsions causes a definite increase in basal metabolism, we were interested to know whether any response could be incited within the gall bladder by the intravenous injection of these emulsions. There would, perhaps, be no occasion for the discharge of gall bladder bile since the gastrointestinal tract was inactive; and yet if the contraction of the viscus was due to an absorbed fatty constituent acting through the blood stream, then a response could, perhaps, be induced by the presence of the fat in the emulsified or the digested state within the blood stream. In these observations, we have used emulsions differing somewhat from that employed by Whitaker. In most of the experiments we have used highly emulsified olive oil or dog lard, the latter obtained by rendering dog fat. These two fats were emulsified in three different types of mediums: 5 per cent gum-acacia solution, 2 per cent aqueous lecithin solution and autogenous blood serum. These emulsions were prepared with and without the bile salt, sodium glycocholate (Merck), known to be without effect on the gall bladder. When the sodium glycocholate was used, it was administered in amounts equal to 0.05 gm. for each kilogram of body weight. Accordingly, six different emulsions were employed in the study and the quantities of fat varied, ranging in volumes equivalent to 0.5, 1 and 2 gm. for each kilogram of body weight. In a few experiments the dog fat was partially digested,

previous to its use, by an alcoholic extract of canine pancreas. Several observations also were made on animals following the intravenous injection of an emulsified preparation of egg yolk and cream.

The detailed method of preparation of these emulsions will be given in a future paper and only the general procedure outlined here. A weighed amount of melted dog lard or olive oil was poured into the emulsifying medium which had previously been warmed except in the case of blood serum which was used without warming. The mixture was then put into a mechanical shaker for thirty minutes to one hour. At the end of this time the emulsion was put into a small separatory funnel and allowed to stand ten minutes and then separated from the excess water which rises to the surface. When sodium glycocholate was used it was dissolved in 3 to 5 cc. of water, heated, and then added to the fat or olive oil with constant vigorous stirring, so that a homogeneous mixture was obtained; following this the emulsion was prepared as usual. When partially digested fat was employed, an alcoholic extract of canine pancreas was added to the fat and bile-salt mixture and digested for about twenty-four hours at 70° C. The alcohol was removed by aëration and the emulsion prepared, as has been outlined. The emulsions of egg yolk and cream were prepared by thoroughly mixing the egg yolk and cream, shaking for about ten minutes, centrifugalizing and employing the upper portion of the mixture. The emulsions prepared in blood serum and 2 per cent lecithin are the most satisfactory from the physical standpoint. Fat emulsified in 2 per cent lecithin with or without sodium glycocholate is in a very fine state of division; the particles are much smaller than erythrocytes and show active Brownian movement.

When the preparations are properly made and completely emulsified, the animal is not disturbed when the emulsions are slowly injected into the jugular or saphenous vein. Occasionally too rapid injection may result in increased respiration, accompanied by slight movements. Ordinarily, if the injections are made slowly over a period of eight to fifteen minutes, the animal is not inconvenienced. Fifteen dogs and fifteen cats comprised the series of animals used in this study. Three methods are employed: the lipiodol method used by Whitaker and Boyden, the common duct intubation, and the direct observation. The first of these is perhaps the best in that it permits the recognition of degrees of emptying and slight tonic changes.

**Experimental Observations.** The dog-fat bile-salt acacia emulsion was given to three dogs. Under ether anesthesia, the bile was withdrawn from the gall bladder of two of these and lipiodol was injected in its place. The common duct in the third dog of the series was intubated and the rubber catheter brought to the exterior through a small stab wound. The dogs were fasted twenty-four hours follow-



ing the surgical preparation, when cholecystograms of the dogs that had been given lipiodol still showed well-filled gall bladders. The emulsion, containing 1.5 gm. of dog fat for each kilogram of body weight, was then slowly injected into the jugular vein over a period of fifteen minutes. Cholecystograms were made 5, 15, 30, 60 and 90 minutes after the injection. Slight tonic changes were periodically visible over the gall bladder during this period. Slight changes in shape or contour were noted and yet lipiodol was never visible in the cystic or common ducts. These slight tonic changes, rhythmically appearing, have been frequently noted and probably do not bear any relation to the injected emulsion. Following the intubation of the common bile duct in the third dog of the series, samples of bile were collected every five minutes for one hour. The emulsion, comparable in fat content to that mentioned, was injected slowly into the jugular vein over a period of fifteen minutes, during which time the animal remained quiet. Samples of bile collected before and during the injection were comparable both in volume and in concentration of pigment. Toward the close of the injection a slight increase in concentration suggested the discharge of gall bladder bile, but in quantities so slight as to be insignificant. Following the injection, five-minute samples of bile likewise compared favorably both in volume and concentration with those taken prior to giving the emulsion, and one must conclude that the intravenous fat injection is without significant effect on the gall bladder.

Intravenous injections of olive-oil emulsions to which was added 0.05 gm. of sodium glycocholate for each kilogram of body weight were given to six dogs. Four of the dogs had been prepared for cholecystographic studies by the lipiodol injection, one had a common bile-duct intubation, and the gall bladder of the sixth was observed directly following the intravenous injection of the emulsion. Cholecystograms taken at successive intervals following injection did not reveal appreciable change in the contour of the gall bladder. Slight changes in shape are visible, but these do not bear any relation to the emptying of the vesicle, for lipiodol was not visible in the cystic or common ducts. A cholecystogram taken one hour following egg yolk and cream by mouth shows the vesicle nearly empty. Bile collections from the intubated common duct of the animals of this series were not appreciably changed following the injection of the emulsion. For two hours preceding the injection, five-minute samples averaged 2 cc. of clear amber bile. During the injection and for twenty minutes thereafter, bile ceased to flow; then gradually there was a return to the average volume. Collections were continued for two and a half hours following the injection, but there was no indication that bile had been expelled from the gall bladder.

Three dogs were tested, following preliminary preparation with lipiodol, with the dog fat emulsified with a 2 per cent aqueous lecithin solution. The emulsified dog fat, partially digested with an alcoholic pancreatic extract, was given to one of these three dogs. In these animals, either with or without the addition of the pancreatic extract, we were unable to recognize any marked changes in the gall bladder following intravenous injection of the emulsions. Subsequent oral administration of egg yolk and cream, however, was effective.

A single experiment was tried by using an emulsion of pure olive oil, and in this, as in all others of our series, the gall bladder did not empty. A single observation was also made on a dog that was given an emulsion of dog fat, which had been subjected to the digestive action of an alcoholic pancreatic extract, and to which a known quantity of sodium glycocholate was added. Slight tonic changes only were visible but lipiodol did not enter the cystic duct.

In the fifteen cats used for this study only two had been prepared previously for cholecystograms by the injection of lipiodol. All others were explored at successive intervals following injection and direct observations were made on the gall bladder. The direct observation has certain advantages in that one may see at a glance the actual state of collapse of the vesicle, and may actually locate the bile expelled. On the other hand, slight changes cannot easily be recognized. However, we were not concerned with qualitative reactions or with degrees of emptying; we rather wished to know whether the gall bladder would expel any bile when fat is introduced into the blood stream. Accordingly, the necropsy method proved entirely satisfactory for our purpose.

The cats previously prepared by the injection of lipiodol were given 3.7 cc. for each kilogram of the olive-oil sodium-glycocholate emulsion through the saphenous vein. Cholecystograms made at 5, 15, 30 and 90 minutes showed slight tonic changes manifested by changes in the shape of the vesicle, but lipiodol was never forced out into the ducts. That the duct system was patent and physiologically functional is shown by the fact that a cholecystogram taken one hour after feeding egg yolk and cream showed a contracted gall bladder with the oil distending both cystic and common ducts.

Resort was then had to the necropsy method. A series of cats was given intravenous injections of emulsions of both olive oil and dog fat in lecithin or serum, to which was added, in either case, a known volume of bile salts. Injections were again slowly made through the saphenous vein, over periods ranging from five to eight minutes. The animals were killed at successive intervals, up to an hour following the injection, and the gall bladder and gastrointestinal tract were immediately explored. Prior to injection the animals were fasted for eighteen hours, so that the vesicles should be well

distended at the time of injection. Necropsy data, following intravenous injection of either emulsion, invariably revealed a well-distended gall bladder containing heavily concentrated bile. Observation of the contents of the gastrointestinal tract from pylorus to ileocecal valve did not disclose evidence of gall bladder bile, and the conclusions were manifest that the gall bladders had not emptied following the intravenous injection of fat.

To determine whether or not the emulsion we were using could cause the discharge of gall bladder bile when given orally, we arranged to feed a similar series of cats with emulsified fats like those given intravenously. Accordingly, the fats were prepared in a similar manner, and quantities proportionate to those given intravenously were given by mouth. In some cases the stomach tube was passed, and in others the animal was given the emulsion through the angle of the mouth so that swallowing was normal. Here again the animals were killed at 5, 15, 30, 60 and 120 minutes after the feeding. Exploration showed in each case that the gall bladder had emptied, and in the longer periods it had emptied completely. An immediate response was apparently set up within the gall bladder, for in the animals explored within five minutes after feeding, the vesicle was partially empty and isolated spurts of gall bladder bile appeared in the duodenum. Exploration at 30, 60 and 120 minutes after food was given showed the gall bladders greatly contracted and concentrated bile at intervals throughout the gastrointestinal tract to the ileocecal valve. The occurrence of concentrated bile at different levels throughout the gastrointestinal tract suggests that the discharge from the vesicle had occurred in more or less rhythmic spurts and not as a continuous discharge.

**Comment and Summary.** These observations on the gall bladders of cats and dogs following the intravenous and oral administration of certain emulsions of fat show rather definitely that contraction of the gall bladder does not take place when these emulsions are injected directly into the blood stream. This is true whether or not the fats are partially digested prior to the injection.

This is at variance with the observations of Whitaker<sup>12,13</sup> following the intravenous injection of an emulsion of olive oil. We are at a loss to explain the disparity in our results. Both in cats and dogs, using either method of study, we were not able to conclude that active contraction of the vesicle occurred. Minor changes in contour, indicating tonic variations, were manifest, but lipiodol was not forced into the cystic duct by these changes. The fact that Whitaker also secured partial emptying following the intravenous injection of liquid petrolatum, a substance ordinarily without effect on the gall bladder, when given by mouth, suggests that perhaps factors other than the presence of the fat caused contraction following the intravenous injection of the olive oil. The physical organiza-

tion of the emulsions we employed may be the reason we were unable to secure contraction, and to substantiate Whitaker's observations.

This report covers a series of observations made on the gall bladders of cats and dogs which have received intravenously various emulsions of fat. The emulsions most extensively studied were olive oil and dog fat, in either autogenous serum or a 2 per cent lecithin solution. Emulsions were used either with or without a known quantity of sodium glycocholate. The injections were made slowly through the jugular or the saphenous vein, and the animal ordinarily remained quiet during the entire period. Studies of the gall bladder following the intravenous injection of these emulsions were made by the cholecystographic method following the injection of lipiodol, common-duct intubation, and the necropsy method. The results of these three methods of study are in agreement in that the gall bladders of cats and dogs do not empty when the emulsions of fat described are injected into the blood stream. Slight tonic changes which are noted are considered as insignificant and wholly unrelated to the presence of the fat. Observations made on the gall bladders of cats, following the oral administration of the emulsions described, show conclusively that the vesicle empties in response to these foods in the gastrointestinal tract, and, accordingly, the conclusions are manifest that contraction of the gall bladder is related to gastrointestinal activity either of a hormone or of nervous excitation.

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## RUMINATION IN MAN.\*

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HUMAN rumination has engaged the wonder of many clinicians for three hundred years. William Shakespeare was in his prime when an Italian anatomist, Jerome Fabricius of Aquapendente,<sup>1</sup> set down the first record of this curious perversion of gastric and esophageal function. It concerned a young man who began to ruminate through worry because his father's forehead had sprouted horns. Fortunately for us, Fabricius became more concerned about the rumination than about the horns. Roughly a hundred years later, the famous dePeyer<sup>2</sup> devoted a large volume to *Merycologia* which is now only of historic interest. For any statistical needs our purpose is best served by the pithy contributions of Riesman,<sup>3</sup> Sinkler,<sup>4</sup> and Einhorn<sup>5</sup> in this country; Mueller,<sup>6</sup> Kohlmann<sup>7</sup> and Gulat-Wellenberg<sup>8</sup> in Germany; and Cambay<sup>9</sup> in France. The latter is important though he wrote almost a hundred years ago, because he was a physician and a ruminant.

The synonyms rumination and merycism mean "cud chewing," and are used by physicians to designate the similarity of these human actions to those of certain of the grass-eating animals. Even patients often comment about this. "Human Rumination is not an actual illness, but an ability to regurgitate a hastily eaten meal in large mouthfuls, to resalivate the food, chew it again and reswallow it. This procedure usually begins fifteen to thirty minutes after the meal, lasts from a half to one hour, and occurs fifteen to twenty times within this period. It stops automatically when food begins to taste sour."<sup>7</sup> It is then evidently an exact reversal of the normal—unchewed or very palatable food leaves the stomach, ascends the esophagus and is delivered into the mouth where it is either masticated or spat out. Only in very rare instances can it be either voluntarily started or stopped. There is never any nausea and no effort is necessary to bring the food up. In fact, food will often appear in the mouth despite a strong effort of the will to suppress the act. Most ruminants are hasty and large eaters and the size of the meal seems to have something to do with the return of the food and the length of time rumination will persist after eating.

The following patients have been seen during the last three years, most of them in the office of Dr. David Riesman, whose stimulation and courtesy have awakened my interest in this subject. They have been studied as thoroughly as the coöperation of

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the patient would permit, which will explain any evident omission of routine studies.

**Case Reports.**—**CASE I.** Mr. J. C., aged fifty-five years, a real estate dealer of Russian-Jewish extraction, came in January, 1926, complaining that his food returned into his mouth. This had been going on for two years but had been worse for six months. It usually began fifteen to twenty minutes after every large meal, never after a light lunch, persisting for an hour to an hour and a half, the food coming sometimes in small amounts and sometimes in mouthfuls. The food always tasted the same as when first eaten, was never bitter, and he could recognize the various articles by their taste. He could not choose which food he would ruminate nor could he regurgitate at will. Even belching would not induce rumination. He was a very hasty eater with a voracious appetite, taking half a loaf of bread and three-quarters of a pound of beef at one meal, swallowed in large gulps practically unchewed. A few days before his visit he was able to take a large meal without ruminating by masticating properly. So far as he knew, there were no merycoles in his family nor had he seen anyone who ruminated. He was short and overweight, had ground down teeth, a lightly-coated tongue, tonsils cleanly removed. The abdomen was obese and tympanitic, otherwise negative. The epitrochlear glands were enlarged. Physical examination was otherwise negative.

**CASE II.**—Mr. W. S., aged fifty-nine years, a Russian-Jewish tailor, has had regurgitation from eight to ten years, after heavy meals. It begins ten minutes after eating and recurs every two to three minutes for a half hour. The food tastes the same as when swallowed except coffee, which is usually sour. This man is not a fast eater nor a heavy one. He formerly chewed the regurgitated food and swallowed it; now, he often spits it out. He has no epigastric sensation of any kind while ruminating, he does not know why he may have originally begun to ruminate and neither of his parents and none of his children have this faculty. He cannot bring food up at will nor has he any selective power over the returned food. He is an undersized, spare individual—there is a good deal of “gold work” in his mouth, his abdomen is normal, and his reflexes normal. His gastric analysis shows free hydrochloric acid ranging from 10 in the fasting contents to 60 after an hour and a half, with a total acid of 95 at this time.

**CASE III.**—A coal operator, W. A. S., aged sixty-five years, has been under observation since 1917, frequently seeking relief for belching, sour risings or flatulence, more recently for precordial distress and vertigo. In addition, to quote his own words, for three to four hours after a heavy meal “all my life food has returned into my mouth just as sweet as it went down.” The food is reswallowed, he can bring it up at will and has at times brought it back to look at it. He always finds it unchanged, it has a normal taste, but he cannot select the food he desires. There is no familial nor imitative history. He is a wiry individual, well nourished, with diseased tonsils and a moderate amount of “gold work” in his mouth. There is a little cardiac enlargement, a mild hypertension, without evidence of decompensation. His abdomen is somewhat relaxed, the physique is otherwise normal. Since 1923 he has had a yearly gastric analysis, all showing an absence of free hydrochloric acid and a total acid ranging from 54 to 70. His gastrointestinal tract has been Roentgen rayed three times. In 1922 and 1924 there was a marked pylorospasm with a slight retention at six hours. In 1928 the pylorospasm persisted, there were marked rugæ in the pyloric antrum and the duodenal cap gave the appearance as if there were a slight prolapse of gastric mucous membrane into it. The roentgenologist has

raised the question of gall bladder disease, but this cannot explain the rumination, for he states it has been present "all my life."

CASE IV.—In May, 1928, J. R., a Russian-Jewish Hebrew instructor, aged forty-two years, complained of indigestion which he said had been present for ten years. It began between the ages of twenty and thirty when, as a poor student, he could not get the proper food. An hour after his main meal "as regularly as clockwork" his food returns in mouthfuls without nausea and without discomfort in the epigastrium. It tastes the same as when eaten, it never becomes sour and may continue to return until the next meal. He says that being unable voluntarily to control rumination is often embarrassing to him when in company. Meats and fish in rich combination prove especially annoying and for this reason he has cut them out of his diet. There is no hereditary nor imitative history. He is a short, apprehensive individual, very well nourished, with a plate of false teeth above and a partial plate below. Except for infected tonsils his physical examination was entirely negative. Routine Roentgen examination of his stomach and esophagus showed no physical abnormality, though there was a slight amount of phrenospasm and a short initial pylorospasm.

CASE V.—T. R. C., aged sixty-three years, a physician of English birth, has been under observation for ten years, first complaining of hyperacidity and pain, which led to the diagnosis of duodenal ulcer for which he was surgically treated. A posterior gastroenterostomy was done by Dr. John Deaver in 1918. However, he remembers ruminating since the age of ten and has always chosen desserts, such as custard pie or fruit cake and especially marshmallow-flavored foods. He emphasizes the pleasure he derives from rumination and says that it amounts to doubling the enjoyment of a good dessert. In earlier life the food was returned within half an hour after eating and continued at intervals of two to three minutes until the food became sour. Of late years the interval of return has lengthened, now being between five and ten minutes. Formerly, he was able voluntarily to bring back desired food; now he ruminates occasionally unexpectedly. It has always been a source of embarrassment to him and he takes great pains to hide the procedure from others. For eight years preceding his first visit to our office he had periods of exacerbation of ulcer symptoms, during which he never ruminated, but the faculty would immediately return as soon as the dyspepsia disappeared. For two years following his operation he was unable to ruminate. Since then he has been able to do it with his old-time zest. He is short and wiry. He has almost an entire set of false teeth, scars of the abdominal operation, but is otherwise normal. Routine Roentgen ray of the upper gastrointestinal tract showed the stomach normal in size and shape, peristalsis good, and a gastroenterostomy opening on the greater curvature through which the barium passed freely. A small amount also passed through the pylorus.

CASE VI.—The most interesting case of this series is that of Hadji Ali, an actor. This performer, whom I have had the good fortune to observe, was born in Cairo, Egypt, and is now between thirty-five and forty years of age. He is short, stocky, exceedingly well-developed and well-nourished, with a tremendous abdominal musculature. Routine physical examination revealed no abnormality.

To being his act, he swallows fifty glasses of water, stands before a trough and without apparent effort brings the liquid up again. He then swallows thirty hazel nuts and an almond and brings up the number of hazel nuts stipulated by the audience before bringing up the almond. He then brings



FIG. 1.—Film of H. A. immediately after swallowing barium. Cardia and pylorus open, stomach and small intestine simultaneously filled. Film taken in recumbent posture.



FIG. 2.—Film of H. A. after voluntary emptying of the stomach. The small intestine is still completely outlined. The small barium shadow in the stomach is a residue pushed back from the intestine by the roentgenologist (see text). The linear shadow is a suspender buckle.





up the remainder of the nuts. Here, I believe the selection is done in the mouth. Next he swallows three handkerchiefs of different hues and brings them back singly in the rotation desired by the audience. I feel confident that these are flavored, enabling him to make selection in the mouth; however, he states that by long practice he has trained himself to stow the handkerchiefs in different portions of the stomach and by exerting pressure through the appropriate abdominal muscle groups, he can bring up the one desired. Finally, he swallows a pint of water and a half pint of kerosene, then stands about 6 feet from a candle burning in a brass box open at the front. The kerosene being of lower specific gravity is brought up first, in small jets which dramatically burst into flame as they approach the candle. When the kerosene is exhausted the water spraying from his mouth apparently quenches the flames.

Rumination in infants and imbeciles is quite as common as it is rare in adults. It may be related to the "cage sicknesses" of childhood, such as head banging and nail biting. Others describe it as merely an occupation to while away the time.<sup>10</sup> The chief argument for this latter view is that infants never ruminate when they are being amused or when they know they are being watched. In some children rumination becomes a serious feeding problem, for they spit out the returning food and lose weight as a result. This habit can be overcome in a very short time by the use of a Siegert balloon sound, which acts as an effective cork for the cardia after meals.<sup>11</sup>

Many writers have stressed the hereditary aspect in the tendency to rumination, but in this series only the actor had any history of the sort, and in this instance it had skipped the parental generation. Both Mueller<sup>6</sup> and Runge<sup>12</sup> have reported so-called "rumination families." Mueller described a father who died of scirrhus carcinoma in the constriction of an hour-glass stomach, who had ruminated for at least fifteen years and whose two sons were ruminants without the knowledge that their father was so afflicted. Runge recorded a grandfather, son and a grandson who were ruminants, each without the knowledge of the other. In both of these families it is evident that there was no conscious imitation and in the series here reported, I could find no instance in which the patient had seen another ruminant.

To gain a concept of the mechanism of rumination we must review our knowledge of the physiology of the upper digestive tract. Food delivered to the esophagus by the pharyngeal constrictors is propelled down its length by regular peristaltic motion under the control of the vagus nerve. Cannon<sup>13</sup> has shown that a bolus passing downward is held at the cardia until a second swallowing act is performed which constitutes the stimulus for the relaxation of the sphincter, allowing food to enter the stomach. Therefore, we should expect that just prior to rumination the patient should swallow. Toussaint<sup>16</sup> has observed it in the herbivora, and I can record this observation in man. The actor always goes through a

swallowing motion just before the gastric contents return. During gastric digestion, the cardia is in a state of tonic contraction, and in some individuals even very strong retching movements are insufficient to relax it; in others stimulation of certain portions of the mucous membrane of the mouth, swallowing, or even a disagreeable psychic influence will be sufficient for relaxation. Ruminants must obviously fall in this group.

There is one extremely interesting and important observation on the action of the cardia in the cat, which was made by Cannon in 1902.<sup>14</sup> He noted with the Roentgen ray a rhythmic regurgitation from the stomach into the esophagus. "The barium mixture runs up to the level of the heart and sometimes even into the neck and then back again. It takes place without any sign of reverse peristalsis and seems to be due to quick contraction of the lower esophagus." Unfortunately, no one has been able to reproduce the results in check-up experiments.

Since the advent of the Roentgen ray the pathologic anatomy of these patients has been more often noted. Autopsies had been hard to obtain, infrequent and inconclusive. Riesman's case showed nothing abnormal. Berg<sup>15</sup> reported a complete spindle-shaped dilatation of the esophagus. The father in Mueller's family showed an hour-glass stomach with a carcinoma at the site of the constriction and an esophagus dilated to the diameter of the small intestine. From the few reported autopsies, we can assume nothing definite.

It is important to note that in the majority of human routine Roentgen ray studies the stomach was found to be normal in size, shape and motility. In contrast to this, the stomach of ruminant animals is divided into four anatomic chambers of which the first two are merely receptacles for food, which will be rechewed when the animal finds the leisure to do so. To carry the comparison a step further, we find that the mechanism is also different with them. Toussaint<sup>16</sup> made an exhaustive study of the pressure changes in the thorax, trachea, upper respiratory tract, and rumen of the cow in the act of rumination. Even fifty years later one must pause to pay sincere homage to his skill, technical cleverness and untiring patience. By a series of superimposed simultaneous, kymographic records of the pressure variations in all the above areas he proved beyond argument that—

1. As rumination commences the diaphragm descends and is fixed. The glottis is closed and the ribs rise, all tending to lower the intrathoracic pressure to a very appreciable degree.

2. The rumen (proximal gastric pouch) is passive during the entire act.

3. The returning bolus must be quite fluid and is aspirated out of the inert stomach by the influence of the suddenly lowered intrathoracic pressure.

The conclusions I will draw regarding the mechanism of human

rumination are based on fluoroscopic observation of two of this series while they were ruminating. This was done through the courtesy of Dr. Henry Pancoast of the Hospital of the University of Pennsylvania and his associate, Dr. Karl Kornblum.

It will be recalled that Dr. T. R. C. had a predilection for eating marshmallow desserts twice, and this was a help in the preparation of the barium mixture. We used the ordinary amount of barium in a water suspension flavored with marshmallow whip. Our first attempt was a failure, because the mixture settled to the bottom of the fasting stomach and promptly disappeared through the artificial stoma. Two weeks later the technique was changed and he was given the same mixture an hour after a heavy breakfast. This time he ruminated well. We only saw the barium in the esophagus once, half way up and so no conclusion can be reached from this, but in the recumbent posture we were able to note significant changes in the stomach. It seemed that most of the food was held in the upper pole of the stomach, giving the effect of an inverted pear. Whenever rumination occurred there was a general contraction of a squeezing type, which relaxed when the act was over. In each instance, the mixture ascended the esophagus so fast we could not see it, but there was no doubt in our minds that the upper portion of the stomach was contracting like a bulb and squirting part of its contents into the esophagus.

For the actor no extra preparation was necessary except that a huge amount of the barium mixture had to be used. He drank it out of a pitcher and as the stomach became more and more filled we were surprised to see a large amount of the mixture course through the pylorus into the small intestine. From this it was evident that during his act he must use both the stomach and intestines as a reservoir. Several films were made with the stomach and intestines full. He was then asked to empty his stomach and we saw him hold his breath, then the barium shot into the esophagus and out the mouth in a steady stream. The stomach seemed to be emptying itself in the manner of a distended balloon diminishing in all dimensions equally, thus delivering the barium mixture to the lower end of the esophagus which contracted and relaxed rhythmically. No peristalsis nor reverse peristalsis was noted. This action continued until the stomach was almost empty when he was asked to stop. The roentgenologist was then able to push some of the barium from the intestine back into the stomach and the patient brought this up when asked to. A second attempt to do this was unsuccessful. The behavior of the stomach here is probably a mean of two factors. There is every reason to believe that contraction of the abdominal wall must have played a part in helping a stomach stretched to such dimensions to empty itself. However, when a major portion of the barium was ejected the diminution in size of the stomach continued and it is probable, therefore, that the gastric

musculature was doing its part also. This idea is strengthened because he was able to regurgitate the small amount of fluid which Dr. Kornblum pushed from the duodenum into the stomach.

We may make the following conclusions from these Roentgen ray observations:

1. Pressure changes in the thorax seemed to play no part.
2. During rumination the stomach empties itself by a diminution in size in all diameters, which is probably an expression of both the tightening of the abdominal muscles and the squeezing contraction of the gastric musculature.
3. The bolus is delivered to the mouth by rhythmic strong contractions of the lower portion of the esophagus, which are squeezing in type.
4. No evidence of organic or functional hour-glass stomach or cascade stomach was noted.

Except for two of Kohlmann's cases and the results here shown, adult rumination had not been seen fluoroscopically, mainly because the barium mixture is so unpalatable that the patients will not regurgitate. To overcome this, Kohlmann devised a "barium beef steak" which gave both bulk and flavor to the meal and was well ruminated. He concluded that the stomach seems to take an active part in rumination, dividing itself by a band of contracting muscle into a functional hour-glass form, from the upper portion of which food is shot into the esophagus. We did not observe any hour-glass deformity, but we feel that the human stomach seems to assume more than a passive rôle in the act of rumination. This is in strong contrast to the herbivorous animals whose food seems to be aspirated out of the inert rumen by lowered intrathoracic pressure. Mueller's reported hour-glass stomach, the site of a carcinoma, therefore assumes a new importance. It stresses rumination in connection with an organic hour-glass stomach, and for Kohlmann it raised the speculative question whether the long-standing irritation of a functional hour-glass constriction gave rise to the carcinoma. It shows also that a serious or fatal lesion may supervene in the stomach of a patient already a ruminant and puts us on our guard to inquire thoroughly into the length of time the rumination has been going on.

Allied to rumination is the "nauseless" vomiting seen in certain adults. These individuals can vomit at will without effort or discomfort, but they bring up the entire gastric contents at once. I have an obese female patient, aged fifty-five years, who has been able to do this since she was fifteen, and now uses the faculty as a convenient safety-valve when the gall bladder disease from which she suffers causes upward epigastric pressure.

Practically every observer has been impressed with a neurotic tendency in merycoles. All the men here recorded are fidgety and neurasthenic. The actor once became so excited that he could not

go on with his act and the patient with the persistent achlorhydria is certain at every visit that he is afflicted with various fatal maladies. The stories elicited from ruminants have almost a Münchhausen tinge. They all say the food tastes good, often better than when first eaten; in fact, one reported patient could only enjoy the proper taste of food during rumination. M. J. K. has put his faculty to a useful purpose. For several years he has been kept on a lacto-vegetarian diet for cardiorenal disease. Nevertheless, he indulges his fondness for meat quite often, spitting it out on second arrival in the mouth. As in the case of our physician, some can exercise a selective action and bring back only sweets or solids or highly-seasoned food.

Most ruminants find their faculty very embarrassing and do everything possible to hide it from general observation. Therefore, it is extremely rare to find a man who is eager to give publicity to the voluntary control of his stomach. H. A., the actor, is the first merycole to be recorded in the American literature who earns his living by gastric gymnastics. The only other case of this sort in the general literature was reported from Munich in 1913. He was an actor in a fair at that city and swallowed a large amount of water in which were several live gold-fish and a frog. He would then bring back either gold-fish or frog as the audience desired. The selection was not made in the stomach but in the mouth. If the frog came up first and was not desired it was quickly reswallowed. This man was observed fluoroscopically by Dr. Gulat-Wellenberg, who watched a frog injected with barium descend into his stomach and return again into the mouth. The observation was reported as a medical curiosity and no attempt was made to explain the mechanism.

It may be objected that our actor is an instance of voluntary vomiting, such as was cited earlier; but a review of his history proves him to be a ruminant who has developed his faculty to this astounding degree. The unusual behavior of his stomach he first noted as a boy, when after swimming, the water he had swallowed returned to his mouth at regular short periods. He became notorious among his playmates for this trick and learned to swallow larger amounts of water for their amusement. He states that he was once thrown out of a street café for ordering and drinking an inordinate amount of water. He then came to the attention of an Italian show owner who played him in Italy in a side show and taught him the rudiments of all the tricks which he now exhibits. He is a hearty eater and is especially hungry at the conclusion of each performance, but only remembers involuntarily ruminating solid food in three instances. The interest he provoked among Continental physicians led him to inquire into his family history. Neither of his parents ruminated, but his paternal grandfather whom he never saw was said to have done so for many years. He never saw any individual who could

ruminate. Clinically he is quite unusual in that he has complete voluntary gastric control and can regurgitate either a large or small amount of gastric contents, no matter what their nature.

(As a conclusion to the presentation of this paper, a motion picture of Hadji Ali's performance was shown.)

**Summary.** 1. A series of six human ruminants are described, five of whom were met in clinical practice, the sixth being an actor who permitted studies to be made upon himself.

2. The clinical findings in this syndrome are described.

3. Two of these individuals were observed fluoroscopically while ruminating.

4. The mechanism involved in the act of rumination is suggested.

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### A STUDY OF STOOLS CULTURED FOR ENDAMEBA HISTOLYTICA FOR DIAGNOSTIC AND OTHER PURPOSES.

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DURING the last half-century many attempts have been made to cultivate *Endameba histolytica* and other entozoic amebas in artificial media: but though numerous claims to success have from time to time been made, it is only recently that any methods have been devised which are at once sufficiently authenticated to be credible and sufficiently straight-forward to admit of ready confirmation by workers other than the original claimants. Most, if

not all, of the earlier "successes" are now known to have rested upon a misidentification of the organisms cultivated or to have involved familiar fallacies of observation or interpretation, and as none of them has yet been substantiated, or has been able to bear critical later examination, it now seems unnecessary to review the history of this subject anew.

Apart from certain debatable results announced by Cutler,<sup>1</sup> the first manifestly successful attempt to cultivate any entozoic amebas *in vitro* appears to be that of Barrett and Smith,<sup>2</sup> who cultivated two intestinal species of endameba from cold-blooded vertebrates—*E. barretti* from turtles and *E. ranarum* from frogs. Their cultures of the first species were independently examined by Taliaferro and Holmes,<sup>3</sup> with entirely confirmatory results; while a full account of the cultivation of *E. ranarum* has also been published by Barrett and Smith<sup>4</sup> and verified by Taliaferro and Fisher.<sup>5</sup> While the method devised by Barrett and Smith appears to be adequate for the species which they studied, it does not seem to be adaptable to the cultivation of all entozoic amebas.

In 1924, Boeck and Drbohlav<sup>7</sup> announced that they had succeeded in cultivating *Endameba histolytica* by an entirely different method, and since the publication of their early papers many independent workers have been able to confirm their results.

Under the direction of Dr. F. M. Johns, Director of the Laboratories of Clinical Medicine in Tulane University, I have cultivated one strain of pathogenic ameba, *E. histolytica*, through 86 subcultures since June, 1928, many different strains of *E. histolytica* were initiated and studied in culture, and numerous attempts were made to perpetuate cultures of other nonpathogenic amebas obtained from the routine microscopic and cultural examination of a large number of specimens of feces.

**Composition and Preparation of Culture Media.** In obtaining and maintaining a large number of cultures of *E. histolytica* many details of producing a uniformly successful medium have been studied. We have tried all of the probable variants based on the original medium of Boeck and Drbohlav. Although this medium is apparently suitable for cultivation and propagation of amebas, it did not give uniformly successful results for routine cultures of stools for the purpose of diagnosing the presence or absence of pathogenic amebas. Dobell and Laidlaw's<sup>6</sup> modification of Boeck and Drbohlav's<sup>7</sup> original media for the isolation and cultivation of amebas was found to be apparently more suited to routine use. This medium furnishes a definite source of assimilable carbohydrate as food for the amebas, and further provides a mild bacteriostatic agent (acriflavine) which may be used to inhibit the growth of such frequently found bacterial flora as would preclude the obtaining of an initial positive culture. In our work we have sought to develop this modification in order that it could be used in the average labora-



tory for routine diagnostic purposes. The following method, in detail, of preparing this modification of Drbohlav's media has seemed to give uniform results:

**I. Ingredients of Media.<sup>8</sup>** (a) *Scrum-Ringer Solution*. Beef or human blood is obtained. After clotting it is placed for twenty-four hours in a refrigerator. The clear serum is pipetted off and mixed with Ringer's solution in the proportion of one part of serum to eight parts of Ringer's solution. Sterilization is accomplished by passing the fluid through the *large* type Seitz-Wertz filter, which permits the fluid to pass only through the filter pad. Filtration is accomplished by use of full vacuum. The filtered, sterile, diluted serum is immediately pipetted off with a 50-cc. sterile pipette and placed in sterile flasks 50 cc. to each flask. These flasks are kept at 8 to 10° C. until ready for use. Inactivation of the mixture (56° C. for thirty minutes) is not necessary.

(b) *Starch*. Rice starch possesses the necessary uniformly small grains which are readily ingested by the amebas, and further is not easily hydrolyzed when suspended in fluid. The method of sterilizing the starch without charring or disintegrating and rendering it soluble has presented quite a problem. Dobell and Laidlaw state that, "After various trials we have found, contrary to the indications in some works which we have consulted, that solid rice starch can be completely sterilized without being charred, disintegrated or rendered soluble, by subjecting it to a temperature of 180° C (dry heat) for one hour. It should be dry before heating and heated in small quantities, not in bulk." An attempt was made to carry out these instructions in every detail. By the method outlined above, we found that rice starch was charred slightly and rendered more soluble. It was found that even as low a temperature as 130° C. (dry heat) for thirty minutes would char and render the starch soluble; which enables it to be readily utilized by the starch splitting bacteria in the cultures. As a result the media became highly acid in a short time and the amebas inoculated grew poorly and often were overcome by bacterial growth.

The following method of sterilization was developed which apparently fulfills the requirements and has given entire satisfaction:

The starch is weighed out in 0.2 gm. quantities, placed in small soft filter paper tubes which are made by rolling a 3½ by 5 cm. piece of thin filter paper about a pencil and in which the starch is kept in place by lightly crimping the ends of the paper tube. The filled tubes are placed in test tubes which are then plugged with cotton and covered with several layers of wrapping paper which is well tied down over the end of the tube, and the whole assembly autoclaved at 15 pounds pressure for fifteen minutes. After autoclaving, the paper covering is removed and the tubes are placed in a hot air oven or incubator to evaporate the little moisture that may have condensed upon the walls of the tube.

(c) *Acriflavin Solution*. A 1 per cent solution of acriflavin is prepared and sterilized in the Arnold sterilizer. Acriflavin solution keeps fairly well when protected from light and at a low temperature.

(d) *Egg Base*. Four eggs are emulsified with 50 cc. of normal saline and poured into 1½ by 15 cm. tubes to a depth of approximately 2 cm. The tubes are placed upright in the water bath and heated to 80° C. for sufficient time to coagulate to a firm consistency, after which they are autoclaved at 15-pounds pressure for fifteen minutes in the upright position. Amebas grow best upon a flat surface.

**II. Assembly of Media.** (a) The starch is added (0.2 gm.) to the serum-Ringer solution (50 cc.) by placing the small paper tubes into the flask. Slight agitation opens up the paper and liberates the starch.

(b) Acriflavine is added by transferring 0.1 cc. of the 1 per cent solution to 50 cc. serum-Ringer starch, which gives an ultimate dilution of 1 to 50,000. Some samples of acriflavin require a greater concentration (1 to 25,000) to retard the growth of unfavorable flora.

(c) Four to 5 cc. of sterile serum-Ringer's solution plus the starch and acriflavin are then poured into the tubes containing the coagulated egg. The tubed culture media should be stored in the refrigerator until used. At the time of inoculation the media should be warmed to 37° C. An equal number of tubes should be prepared, omitting the acriflavin.

The pH of the prepared media varies from 7.2 to 7.8 and needs no adjustment, this being the optimum range of hydrogen-ion concentration determined for *E. histolytica*.

Drbohlav advocates the addition of 5 gm. per liter of potassium acid phosphate to the media which is adjusted to a pH of 7.4. This, we have found, to be unnecessary as the medium is capable of adjusting itself to the original pH even after forty-eight hours of bacterial growth which tend to form organic acids. We have found, as Dobell and Laidlaw, that alkalies as well as acids are injurious to growth of endameba in direct proportion to their concentration.

**Method of Inoculating, Examining and Transplanting Cultures.** A particle of fecal material about 1 or 2 mm. in diameter is picked up on a wooden applicator and is transferred to a tube of plain, and a tube of acriflavine charged media which have been warmed to about body temperature.

With soft or dysenteric stools, which are more apt to contain vegetative amebas, the material used for inoculation should be obtained fresh from the patient. Proctoscopic removals and rectal washings should, similarly, be inoculated immediately.

With formed or hard stools, which are more apt to contain cysts, the cold stool will suffice even though it be several days old. We have obtained the same results with cysts fresh from the patients or with those kept in the refrigerator for several days.

The tubes are incubated in an upright position at 37° C.

Maximum growth is usually seen on the third or fourth day of incubation. On the fifth or sixth day the amebas usually die unless they are transplanted into fresh media. Under cultural conditions very few amebas encyst, but with frequent transplantation they can be propagated in the vegetative form for an unlimited period.

Examination of the cultures is made by skimming the débris of starch and bacteria from the surface of the coagulated egg with a capillary pipette having a large lumen (1 mm.) which has been scratched and broken to present a square tip. Use a Wright's rubber bulb to produce suction. A fraction of a drop of material is removed, placed on a slide, cover glass added, and examination made with the 16-mm. objective.

To transplant the culture a drop of the material is transferred to fresh media that has been previously warmed.

**Differentiation of Pathogenic and Nonpathogenic Amebas Cultured.**<sup>9</sup> There is no remarkable change in structural detail or behavior of the amebas in their cultural environment, the main features conforming closely to the accepted descriptions. In culture, however, the unlimited number of amebas available for study permits of greater emphasis being placed on minor individual peculiarities. The nuclear structures as shown by appropriate stains retain the same characteristics exhibited by amebas obtained from their natural habitat.

*I. Endameba histolytica.* Cultivation of this ameba produces a reduction in size, a slowing of activity and a diminution in the clear, glasslike appearance of the ectoplasm which characterizes the organism in stools. In the feces, it is unusual to find bacteria within the cytoplasm, as we often do in culture. The nucleus, usually invisible in the living specimens from feces, is defined with ease in wet preparations from culture. In a way, the general effect is to cause the organisms to resemble more closely some strains of *Endameba coli* as found in liquid feces.

At room temperature the amebas when first removed from the culture are found to be rounded and motionless, but movement begins after an interval of several minutes. This movement is highly characteristic. It is comparatively swift, progressing at about 30 microns per minute. It is fairly definite in direction; it is as if one had the impression that the ameba has a purpose in moving and that it is not to be delayed en route.

The shape of the ameba in movement is also important. Viewed with the low power of the microscope, the appearance of a large number of quadrilateral objects in motion is highly characteristic. Viewed with the oil-immersion lens the margin of the ameba is seen to be smooth with the clear ectoplasm more or less well differentiated from the endoplasm. With careful attention to light and focusing, the nucleus can be identified by the appearance of a refractile ring

of granules, like a string of beads. The karyosome cannot usually be defined; if defined, it is seen to be a tiny dot, usually central in position. The appearance of the karyosome, or rather, the lack of its appearance, is a most important factor in the identification, as in *E. coli* the karyosome may be seen as a large eccentrically placed granule with a nuclear ring composed of large highly refractile granules.

The small races of *E. histolytica* are essentially similar to the larger strains. On account of size, one may confuse them with *E. nana*, *I. williamsi*, or *D. fragilis*. However, by a careful study of the movements and structure, one should easily be able to make a diagnosis. It may be necessary to stain these smaller amebas before reaching a conclusion as to identity. Subcultures of *E. histolytica* tend to show more characteristic forms, while the non-pathogenic amebas will hardly grow at all, and are soon lost on this particular media.

Encystment of *E. histolytica* in culture is of too infrequent occurrence to be of value in diagnosis. Cysts were produced irregularly, some strains producing numerous cysts on the third or fourth day, while with other strains cysts were seldom or never found. The cysts in culture were identical with those observed in feces—the glycogen content being particularly high. Culture-produced cysts were capable of initiating fresh cultures after being kept for thirteen days at 8° C.

*II. Endameba coli.* This ameba has a tendency to succumb in culture; that is, in the medium prepared as described most strains did not survive the first transplant. I have come to regard this as a point of some value in differential diagnosis, as *E. histolytica* is usually easily maintained in culture.

The majority of the strains observed lacked the characteristic motion of *E. histolytica*. At room temperature (70° F.) there is little tendency toward progressive movement; they prefer to merely change shape, lolling about in practically the same position. The outline of the ameba is rarely quadrilateral as is characteristic of *E. histolytica* but is inclined to be irregularly circular. There may or may not be a sharp differentiation between endoplasm and ectoplasm; when closely compared, there is little difference from that observed in *E. histolytica*. The marginal outline is smooth. Visibility of the nucleus is good as a rule. When visible, the presence of a large eccentrically placed karyosome is the concluding feature of the diagnosis. They are more prone to ingest bacteria, while *E. histolytica* are usually satisfied to gorge themselves with starch granules.

*III. Iodameba Williamsi.* The size, characteristic movement, marginal outline, and the visibility of the nucleus of this ameba are sufficient to permit diagnosis from a study of the living cell. It is considerably smaller than *E. histolytica*, so much so that a search

with very high magnification is necessary to determine their presence in a culture. The movement is very slowly progressive, indefinite in direction and somewhat listless in execution. The marginal outline of the well differentiated ectoplasm in some stage of the movement is found to possess coarse serrations, a characteristic not observed in other amebas included in this work. The karyosome is practically always visible as a large highly refractile object resting in a clear area. With care in distinguishing these points, there should be little confusion with *Endameba nana*, with which it is most likely to be confused.

*IV. Endameba nana.* All strains obtained in culture were small, measuring about 9 microns in diameter. The character of the movement and form in movement very closely resemble small races of *E. histolytica*. The pseudopodia are well differentiated and consist of ectosarc. The marginal outline is smooth. Progressive movement is fairly rapid. However, the large karyosome of *E. nana* is usually plainly visible as a large highly refractile inclusion. The presence of the latter feature in an ameba resembling small races of *E. histolytica* should be sufficient to make a diagnosis.

**The Influence of the Bacterial Flora upon the Initial and Subsequent Growth of Amebas in Culture.**<sup>6</sup> "Pure cultures" of amebas, such as can be obtained by the Boeck-Drbohlav technique and its various modifications, are "pure" in the sense that they contain one species of ameba alone; but they inevitably consist of amebas accompanied by a diversity of bacteria (and possibly other micro-organisms). *E. histolytica*, and all other species studied, largely depend in cultures upon these associated organisms for their food supply and it does not seem feasible to eliminate them entirely.

Strains of amebas initiated from free forms in feces are always accompanied by a great many different bacteria derived from the intestinal contents. For the cultivation of many of these bacteria the various media employed are often excellently suited; and consequently they are propagated, along with the amebas, whenever subcultures are made, but it always happens that the bacterial flora originally present in initial cultures undergoes considerable changes as regards the species and their relative proportions on continued cultivation. For a variable number of generations the flora fluctuates, finally reaching a state of stable equilibrium by a process of natural selection. In this process the amebas may sometimes be exterminated, and for this reason freshly isolated strains of amebas may require careful watching for some time before they begin to grow with regularity. During this period in the presence of rapidly-growing unfavorable bacteria frequent transplants to fresh media is the most important consideration. Growth under constant conditions of media and temperature can be foretold with certainty.

Obtaining of primary cultures of amebas by methods involving such a number of unknown variables, which sort themselves out, in the end by chance, is obviously unscientific. Success often depends largely upon luck. It is therefore clearly desirable to discover some means of controlling the composition of the entire bacterial flora at will; but this has been found to be extremely difficult.

That the bacteria in a culture of amebas exercise a profound influence upon its welfare, no one who has attempted to cultivate these protozoa can doubt. It is only necessary to have acid-forming bacteria present to convince the most skeptical. Such organisms, by acidifying the medium to a degree which the amebas cannot tolerate, may wipe out a flourishing culture in a few hours. For example, starch-splitting bacteria, if introduced into cultures containing this carbohydrate, soon make further cultivation of the amebas impossible; but if they are exterminated by passage through acriflavin-containing media the culture may be carried on indefinitely.

**Immunologic Reactions Possible with Cultured Amebas and Extracts of These.** Recently C. F. Craig<sup>10</sup> has stated that he has found that immune substances are produced of which he can obtain evidence by serologic reactions. The development of a complement-fixation test, which would be specific, would indeed be welcome. Especially in some cases of suspected liver abscess where a diagnosis, at present, can hardly be made except by surgical intervention.

We have endeavored to investigate the problem from the viewpoint of allergic skin reactions using glycerin extracts of luxuriant cultures of *Endameba histolytica*. Glycerin in strength of 90 per cent was used to extract the organisms. Cultures were centrifugalized at low speed for about fifteen to twenty seconds. The sediment upon examination showed that there was approximately an equal volume of *E. histolytica* with the bacteria and starch. This sediment was then mixed with an equal volume of 90 per cent glycerin. The mixture was allowed to remain in the incubator for three days, followed by careful centrifugalization at high speed. The supernatant fluid was carefully pipetted off and tested for sterility by inoculating bouillon tubes. The sterile extract was injected intracutaneously (0.2 cc.) into a number of patients known to have amebic infection, and an equal number of controls in whom no evidence of infection could be found. In all of those patients known to have the infection, the skin test was positive. A positive reaction consisted of a small bleb about 2 mm. in diameter surrounded by a red areola about 1 cm. in diameter. In those patients in whom by ordinary laboratory methods *E. histolytica* could not be demonstrated, reactions were seen varying in intensity from a completely negative one to a reaction similar to those obtained in the infected patients. We have sought an explanation for this, and it seems

plausible that besides extracting the antigenic properties of *E. histolytica*, such a crude extract must contain peptone or other split protein products which would occasionally give a nonspecific reaction. The use of alcohol as a menstruum as recommended by F. C. Craig seems to eliminate the factors giving nonspecific reactions. He states that alcohol extracts the antigenic principles of *E. histolytica*, but does not extract those organisms which produce the nonspecific reaction; namely, certain strains of streptococcus. We have not employed alcoholic extracts as yet; however, it seems to be of quite a distinct value and an effort will be made to confirm Dr. Craig's observation using such antigens in cutaneous tests.

**Diagnostic and Differential Diagnostic Aids Made Possible by Culturing Feces for Amebas.** In the discussion of the composition and preparation of the culture media, mention was made of the practical application of the method in the clinical laboratory. In the examination of stools for the presence of the various forms of *E. histolytica*, one cannot always make a certain diagnosis. Cysts are sometimes encountered which are atypical or the *number* present may be extremely small, and a diagnosis by the ordinary routine methods is most difficult even with the employment of appropriate stains. Properly-stained wet-fixed smears are superior to the ordinary intravital staining with iodine we admit, but this requires not only considerable technical ability to stain, but much valuable time in finding amebas after staining, as well. Therefore, a method which may be employed in the ordinary clinical laboratory and one which does not require a great deal of time would be of quite an advantage. With the cultural method both atypical cysts and immobile vegetative forms may be propagated and their characteristics studied in culture. In this way careful and detailed study is possible and a positive diagnosis can be made in nearly all instances.

One can readily see that in the case where only a very few of the organisms are present microscopic examination of the fresh specimen may not reveal them, here the cultural method should prove of considerable aid, in that although only one or two organisms may be originally introduced, examination of the culture at the end of forty-eight to seventy-two hours reveals large numbers of vegetative forms which are characteristic of the species. Therefore, we conclude that the introduction of the cultural method as an aid to the ordinary diagnostic methods will eventually prove to be quite an advance in diagnostic laboratory technique.

**Comparative Diagnostic Results Obtained by Means of Cultures and the Direct Microscopic Examination.** During the past six months, routine stool examination employing both the microscopic and the cultural methods has revealed quite interesting results. During the course of this examination nearly 300 specimens have been carefully considered. A microscopic examination employing

the method advocated by F. M. Johns<sup>11</sup> for the concentration of cysts was made. In the case of diarrheal stools direct microscopic examination was made of various parts of the stool for vegetative forms. A record of the microscopic examination was made and a particle of stool inoculated as outlined above into suitable culture media. After forty-eight hours and again after seventy-two hours the culture was examined for amebas. In cases of *E. histolytica* infection, practically 100 per cent of those which were found to contain amebas by direct microscopic examination also gave a positive growth on culture. On only one occasion has microscopic examination given negative results, and cultivation revealed a positive result. In this case, a liquid specimen from a patient with acute diarrhea was obtained about 10.00 A.M. On two different occasions during the day the specimen was examined by two competent observers with negative results. Examination of the cultures two days later revealed a luxuriant growth of amebas which were characteristic of the species *E. histolytica*.

**The Incidence of Amebic Infection in Louisiana as Shown by a Combined Cultural and Microscopic Study of 258 Patients.** In a recent review of the literature, we have not been able to find any record of the incidence of amebic infection in Louisiana. C. F. Craig<sup>12</sup> states, "It is now quite generally accepted that incidence of about 10 per cent of infection with *E. histolytica* may be expected in carefully-conducted surveys of the population of most localities in the United States; with a *higher* incidence of infection in institutions and in regions along the Mexican border and the Gulf Coast." A routine examination was made of the feces of 50 patients visiting the Outpatient Department of Charity Hospital during the summer of 1928. Specimens were taken regardless of the complaint and in the order in which they presented themselves for medical advice. The remainder of the patients, 258 in number, were selected from the clientele of F. M. Johns and from the students of the present junior class in the Tulane School of Medicine. Six of the patients from Charity Hospital were carriers of the encysted form of *E. histolytica*. Five of the patients seen by F. M. Johns were carriers of cysts and 2 of them who were complaining of severe diarrhea with tenesmus had vegetative forms of *E. histolytica* in the stool. Of the 108 junior medical students examined 4 had encysted *E. histolytica* in their stools. Thus we have an incidence of 6.97 per cent of amebic infection, either with cysts or vegetative forms, in this somewhat selected group of Louisianians. From this survey we may, in a general way, estimate the incidence of *E. histolytica* infection in Louisiana. Here we have a series of patients from the lower strata of society from Charity Hospital and those from the higher walks of life and a number of apparently healthy students in the present junior medical class. From these studies



one may conclude, with some conservatism, that the incidence of amebic infection in Louisiana among the general population is probably somewhat below 7 per cent.

**The Importance of a Cultural Method of Examination in the Detection of "Carriers" From a Public Health Standpoint.** The prevalence of the infection of *E. histolytica* has been estimated at approximately 10 per cent in various parts of the United States. Here, in Louisiana, we have found that approximately 7 per cent of the people examined show either cysts or vegetative forms in their stools. In various institutions the incidence may be very much greater, due to the fact that if one of the kitchen force should be a "carrier" that everyone in the institution may take in cysts of *E. histolytica* with their food and subsequently become infected. That the infection is disseminated among the population by carriers of *E. histolytica* is little in doubt.

To determine which are the "carriers" in a community, examination should be made of the stools of all the individuals at approximately the same time. That examination of all the individuals should be done at the same time, should be stressed. If the stools of only a few individuals are examined every day or so and the treatment given these cases, the eradication or even a great reduction in the incidence cannot be hoped for. It is now generally accepted that there is no immunity developed after infection with *E. histolytica*. By the time the survey is complete it is very probable that those first examined are reinfected by those who are last to be examined; especially if the individuals come in contact with food and drink of others.

The task of general stool surveys at first seems quite formidable. The examination of fresh stools for cysts requires the services of a protozoölogist or a technician especially trained along these lines. This is quite an added expense to any laboratory.

With the advent of the cultural method as a diagnostic aid, the examination "*en masse*" may be conducted at the expenditure of only a minimum of time and effort on the part of the health department laboratory.

The method of inoculating, examining and transplanting the cultures has been described and its simplicity of practical application is obvious. The cultural method may be used by the average technician in the laboratory. The diagnosis of the amebas in culture is quite easy.

The problem of diagnosis of carriers of amebic infection is most important for at present we have a specific therapy which is quite efficacious. The cost is moderate and the treatment is not trying on the patient. The rewards, from a public health standpoint, would repay, by many fold, the effort, time and money expended. The efficiency and productiveness of a community is directly proportional to the health of the individuals comprising its population.

**Summary and Conclusions.** 1. The influence of the bacterial flora upon the initial and subsequent growth of amebas in culture is very important, yet it does not seem feasible to eliminate the accompanying bacteria entirely.

2. The factors producing death of the amebas in culture are multiple, each playing its own particular rôle.

3. The immunologic reactions possible with cultured amebas and extracts of these give promise as a valuable aid in diagnosis.

4. The cultural method here described of stool examination for diagnosis of presence of *E. histolytica* has so far been equal to any laboratory means of diagnosis, and may eventually prove superior to the direct microscopic method.

5. From a study of 258 private and dispensary patients and medical students, it is estimated that the incidence of amebic infection in Louisiana is a little below 7 per cent.

6. Use of the cultural method of stool examination for *E. histolytica* would result in considerable saving of time and personnel in public health work in the detection of carriers of *E. histolytica*.

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## INFECTIONS PROBABLY DUE TO MORGAN'S BACILLUS.

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SINCE its first description, in 1906,<sup>1</sup> the pathogenicity of Morgan's bacillus has been much debated. Although Morgan described the organism as a pathogen concerned in the causation of diarrheal conditions, especially in children, his conclusions have never been generally nor entirely accepted, even though his studies were later confirmed by himself and Ledingham,<sup>2</sup> Ohrum and Bahr,<sup>3</sup> and Bahr and Thomson.<sup>4</sup> Subsequent observations have shown Morgan's bacillus to be rather widely distributed, isolations having been made by Kligler<sup>5</sup> and Fridtjof Bang<sup>6</sup> among others, from the soil, roaches, and mice as well as from the feces of healthy and sick individuals. In spite of this, there is increasing evidence that the organism can under certain conditions invade and initiate disease processes in man.

Tribondeau and Fichet<sup>8</sup> and later d'Herelle<sup>9</sup> found Morgan's bacillus in the stools of patients suffering from dysentery. Thjötta<sup>10,11</sup> reports its isolation in ulcerative colitis and fatal cholecystitis: Olaf Bang<sup>7</sup> isolated it from the feces of a patient with intestinal hemorrhage occurring during the course of purpura abdominalis. Magath and Jackson<sup>12</sup> isolated it in a fatal case of septicemia, with pyemia. Riding<sup>13</sup> describes it as a cause of pyelitis. Havens and Ridgway<sup>14</sup> discuss its occurrence as an etiologic factor in 13 cases of pyrexia, all presenting undoubtedly distinct and well recognizable clinical pictures.

It is the desire to here briefly review certain observations that have been made upon various biologic characteristics of Morgan's bacillus and to report its isolation from three human cases, believing that the exact status of the organism as a pathogen will be definitely established only by correlation of the information gained by such reports.

**Morphologic and Cultural Reactions.** Morgan's bacillus is a slender, slightly motile, Gram-negative rod averaging 1 to 3  $\mu$  in length when observed in young bouillon cultures. Large and bizarre involution forms are not uncommon, occurring especially in older cultures grown on agar. The hydrogen-ion concentration range of growth in peptone water for ten isolations studied was pH 4 to pH. 9 S and R colonies were differentiated. All isolations studied produced indol in peptone water, the more recent isolations giving especially strong reactions. Extensive fermentation studies gave regular acid formation with gas production in

glucose, levulose, and galactose peptone water. Browning was noted with acetate agar and no growth in citrate media. Gelatin was not liquefied.

**Pathogenicity.** Investigators agree that Morgan's bacillus is usually nonpathogenic for small experimental animals. Second generation cultures from Case III hereinafter reported were highly pathogenic for guinea pigs and white rats following intraperitoneal injection. This pathogenic power was not resident in cultures of the same isolation eight generations older and tested sixteen months later. Isolations from the other cases herein reported, as well as isolations made during the course of this study from the feces of two healthy children and from the feces of a case of typhoid fever were nonpathogenic for guinea pigs, white rats and mice.

**Serologic Interrelationship.** Immune serums produced in rabbits with the isolations from Cases I and III agglutinated only their homologous organisms. Serum from Case II weakly agglutinated organism from Case I and the Fly strain in dilutions of 1 to 10. Extensive absorption and agglutination experiments, to be reported in detail later, failed to show any serologic interrelationship between local isolations and other available strains. These results are in agreement generally with those of other investigators.

**Case Reports.** CASE I.—L. D., white, female, aged twenty-three years, had malaise, headaches, loss of appetite, for three days before noticing temperature of 104° F. The blood count on the fourth day was 4750 white cells, with 72 per cent neutrophils. Blood culture on the fifth day was positive for Morgan's bacillus. The blood count on the sixth day was 9900 white cells, with 76 per cent neutrophils; on the twelfth day 9000 white cells with 76 per cent neutrophils. Agglutination tests with *B. typhosus* and *B. paratyphosus* A and B were negative on five occasions. There was slight diarrhea after the sixth day. Feces culture was negative for *B. typhosus*, *B. paratyphosus* and Morgan's bacillus on three attempts. Headache and myalgia were marked. There was fever for eighteen days, with marked morning remissions. Homologous isolation of Morgan's bacillus was agglutinated by the patient's serum in dilutions up to 1 to 240 on the tenth day of illness.

CASE II.—A. L., female, aged three years, had had recurrent attacks of pyelitis accompanied by irregular fever for the past two years. The present attack was of four days' duration. The urine showed much pus, with a moderate trace of albumin. Morgan's bacillus was isolated from a catheterized specimen of urine on two occasions. The homologous organism was agglutinated by the patient's serum in a dilution of 1 to 120. There was no agglutination with *B. typhosus*, *B. paratyphosus* A and B, but *B. coli communis* was agglutinated in a dilution of 1 to 10.

CASE III.—A. M., white, female, aged three years, had had severe diarrhea for seven days and had lost some weight. The fever range was 100 to 102° F. There were five to eight profuse watery evacuations in twenty-four hours. Morgan's bacillus was isolated from stool. A homologous culture was agglutinated by the patient's serum in dilutions up to 1 to 200. There was no agglutination with *B. typhosus*, *B. paratyphosus* A and B, *B. dysenteria*, Shiga, Flexner, Hiss Y and Park.

**Discussion and Summary.** It is believed that consideration of the cases here reported points to the strong probability of Morgan's bacillus being concerned as an etiologic factor. Case I has numerous clinical features in common with those presented by the cases reported by Havens and Ridgway. The fever course, although somewhat shorter, generally approximates that of their cases. Headaches and myalgia were common features. No chill at the onset of illness was noted, however, a feature so common in their cases. Isolation of the organism from the circulation and its subsequent agglutination in high dilutions are naturally the most significant diagnostic criteria, and that especially in view of the constant lack of agglutination of other organisms by the patients' serum. Three months after recovery, agglutinins for Morgan's bacillus were not demonstrable.

In Case II, Morgan's bacillus was isolated from catheterized bladder urine on two occasions, and agglutinins were demonstrated in the patients serum for the homologous organism in rather high dilutions. In addition, the organism in Case I and that of another isolation were weakly agglutinated by the patient's serum. Another possible suggestive feature in this case was the rapid recovery and freedom from subsequent attacks over two years after administration of an autogenous Morgan-bacillus vaccine, even though previous attacks had neither been helped nor prevented by stock colon-staphylococcus vaccines.

In Case III, the organism was isolated from the stool and specific agglutinins were demonstrated for it. This feature causes the case to differ from those of Thjötta, who, though able to isolate Morgan's bacillus from the stools and from intestinal lesions at necropsy in cases of severe colitis, was never able to elicit agglutinins in the blood of his patients, not even in nonfatal cases.

The exact place Morgan's bacillus should occupy in the classification of microörganismal forms is still debatable. As Thjötta rightly points out, its inclusion in the genus *Salmonella* is probably not justifiable. It has far more points of biologic differences than similarity with the members of this group. In spite of its fermentation reaction it can undoubtedly be placed more appropriately with the *Escherichia*, with which it has so many common biologic characteristics. Its appellation as *Bacillus metacoli* (Morgani) as suggested by Dutch investigators is justifiable and possibly desirable.

**Summary.** The isolation of Morgan's bacillus in cases of pyrexia, pyelitis and colitis is reported. One strain isolated proved pathogenic for small laboratory animals. Agglutinins were demonstrated for homologous organisms in the blood of all three patients. Observations upon some biologic characteristics of the organism are presented together with a plea in support of Thjötta's position for noninclusion of the organism in the genus *Salmonella*.

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**DIABETES INSIPIDUS AND LESIONS OF THE MID-BRAIN:  
REPORT OF A CASE DUE TO A METASTATIC  
TUMOR OF THE HYPOTHALAMUS.\***

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THE etiology of diabetes insipidus still remains an unsettled problem. The two views chiefly advanced at the present time are first, that it is of pituitary origin and dependent upon a hypofunction of the posterior lobe, and second, that it is of nervous origin and due to lesions of the hypothalamus, particularly of the tuber cinereum or the corpora mammillaria. Although the pituitary conception has had most adherents since 1912, there have been those who have held to the view, based both on experimental and clinical grounds, that, although the posterior lobe of the pituitary may be involved in a tumor or cyst, the actual cause of the disturbance of water metabolism is located in the structures comprising the hypothalamus. The purpose of this paper is to review some of the evidence supporting these two views, and, to report a case of diabetes insipidus in which the pituitary was intact but in which there was a metastatic tumor involving the mid-brain, or hypothalamus secondary to a tumor of the lung.

Before presenting some of the evidence which has been advanced to support the pituitary conception of the etiology of diabetes insipidus, a brief statement concerning the embryology, histology and functions of the pituitary gland may not be out of place. The gland consists essentially of the anterior lobe, the posterior lobe and

\* Read at the meeting of the Association of American Physicians, Atlantic City, May, 1929.

the pars intermedia, an epithelial envelope partially surrounding the posterior lobe.

The anterior lobe is developed from a diverticulum of the ectoderm of the primitive buccal cavity. It is essentially a glandular structure and its function has a very important bearing on growth and on the development of the primary and secondary sexual characteristics of the individual.

The posterior lobe is of nervous origin and is developed as a down-growth from the floor of the embryonic brain. It is essentially made up of what have been considered neuroglia cells and fibers but it was known that columns of cells from the pars intermedia extended into it. Although it had been believed that it presented none of the features of a secretory gland, yet the work of Lewis and Lee<sup>1</sup> recently has shown that it actually contains groups of cells arranged even in the form of a tubuloracemose gland in infants up to four years of age. There is evidence, therefore, that it does contain cells which may perform a definite secretory function. It is important to note that Cushing<sup>2</sup> has demonstrated delicate nerve fibers of uncertain destination passing down the infundibular stalk and becoming lost in the upper portion of the posterior lobe. Previously, in 1911, Cajal had described nerve fibers passing into the neurohypophysis. In 1922, Hoenig reported nerve fibers in the neurohypophysis and stalk, as well as fibers passing through the infundibulum and apparently ending in the epithelial cells of the anterior lobe. These findings are reported by Fink<sup>3</sup> in his admirable review of diabetes insipidus.

Among the chief functions attributed to the extract of the posterior lobe of the pituitary gland are its pressor, oxytocic, respiratory, diuretic—antidiuretic, and melanophore expanding properties. To explain the latter it may be stated that hypophysectomized tadpoles become albinos, but when injected with pituitary extract they assume their normal pigmented color. In addition, the posterior extract influences carbohydrate metabolism acting through the hormone of the islands of Langerhans, and probably has some influence as a galactagogue.

The first evidence advanced to indicate that the extract of the posterior pituitary lobe influenced water metabolism was in 1906 when Schäfer and his associates Magnus and Hering showed that its injection into animals produced a transitory polyuria. Harvey Cushing, in 1910, in removing the posterior lobe of dogs, reported that this procedure was accompanied by transitory increase in the urinary flow.

Shortly after this there began to appear in the literature clinical evidences supporting the same view. The first clinical report was that of E. Frank<sup>4</sup> who, in 1912, reported a case of diabetes insipidus in a man who had been shot and in whom the Roentgen rays showed that the bullet had lodged in the sella turcica.

In 1913, M. Simmonds<sup>5</sup> reported a case of diabetes insipidus in a woman, aged thirty-seven years. Two months after an excision of the breast for carcinoma she developed a very marked polyuria. The autopsy showed, in addition to numerous other metastases, one involving and destroying the posterior lobe of the pituitary gland. This metastasis pressed on the pars intermedia of the posterior lobe but did not involve it or the anterior lobe. Simmonds believed that the polyuria was dependent upon the stimulating effect of the metastasis on the pars intermedia.

Harvey Cushing,<sup>6</sup> in his Shattuck Lecture in 1913, stated that his animal experiments and surgical experience in hypophysial disease strongly convinced him that there was a very intimate relationship between the polyuria of diabetes insipidus and pituitary lesions. Among his first 100 cases of pituitary disease the polyuria had been so marked that in 6 a diagnosis of diabetes insipidus had been made by the physicians referring the cases. He reported a remarkable case (which the writer saw personally) of polyuria in a woman aged forty and totally blind, who presented signs of hypopituitarism. This polyuria, which reached 12 liters daily and was accompanied by an insatiable thirst, followed a sellar decompression operation for relief of symptoms and lasted for a period of three months. Cushing believed that the polyuria resulted from an irritative lesion of the posterior lobe of the pituitary, sustained during the operation.

In 1913, also, important therapeutic evidence appeared which seemed to further substantiate the intimate relationship between the posterior lobe of the pituitary and the polyuria of diabetes insipidus. Von den Velden<sup>7</sup> and Farini<sup>8</sup> independently, found that extracts of the posterior lobe and pars intermedia caused a diminution of the polyuria in diabetes insipidus. Although von den Velden first demonstrated the efficiency of pituitrin, he failed to grasp its significance as a therapeutic agent, stating "there is little to favor the idea of substitution therapy." Farini, on the other hand, accepting the results at their true value, advanced the view that diabetes insipidus was a disease due to hypoactivity of the posterior lobe of the pituitary.

The observations of von den Velden and Farini were soon confirmed by many others and experience has shown that pituitrin, either given hypodermically or by nasal administration as a spray or by soaking pledgets of cotton with pituitrin and inserting them into the nasal cavity, as first advocated by Blumgart, has proven in many cases of diabetes insipidus to be most effective in checking the polyuria and consequent thirst, and is the most effective means we have at our disposal at the present time for relieving the distressing symptoms of the disease.

As has already been mentioned, Schäfer and his associates found that the effect of the injection of posterior-lobe extract was to pro-



duce a diuresis. The work of von den Velden and Farini and others later showed that, although diuresis is the primary effect of the extract, this diuretic action is purely transitory and is soon followed by an antidiuretic effect producing a striking oliguria. Abel's investigations are most convincing on this point.

There has been much discussion as to whether the various actions attributed to the posterior lobe of the pituitary are due to a single or several active principles. Fühner,<sup>9</sup> in 1920, published the result of his work which led him to believe that there were four such principles in the pars nervosa that influenced the organs of circulation and respiration, the kidneys, intestines and uterus.

In 1924, Abel, Rouiller and Geiling<sup>10</sup> reported the isolation of the principle of the posterior lobe as a pituitary tartrate, which they found to possess the pressor, diuretic-antidiuretic, respiratory and melanophore-expanding actions known to be exerted by the extract of this lobe. They showed that this salt, when injected in solution subcutaneously, had the same antidiuretic action as pituitrin possesses in the treatment of patients suffering from diabetes insipidus. Abel believes that there is but one active principle in the posterior lobe and holds that all the pharmacologic actions attributable to the posterior lobe are possessed by his tartrate.

On the other hand, Kamm, Aldrich, Grote, Rowe and Bugbee,<sup>11</sup> following up the work of Dudley<sup>12</sup> in England, claimed in 1928 to have separated two active principles from the posterior lobe, one having a pressor, and the other an oxytocic action, and which they respectively call vasopressin and oxytocin. It is interesting to note that Gargill, Gilligan and Blumgart,<sup>13</sup> in studying the antidiuretic effect of these two principles on normal individuals and in 2 cases of diabetes insipidus, found that it was the vasopressin only that possessed this action.

Whether there is more than one active principle in the posterior lobe of the pituitary or not appears to be as yet unsettled. The experimental work of Abel on his tartrate salt seems so convincing, however, that it will probably be shown that his unity conception will be later confirmed.

How pituitrin exerts its effect is not definitely known. Stehle,<sup>14</sup> as a result of his experimental studies, offers the following hypothesis of its diuretic-antidiuretic action:

"Assuming that the capacity of the tissues to retain water is a function of the electrolyte content or ion balance of the tissues, we might regard the presence or absence of pituitary extract as entailing the following consequences. Pituitary administration causes the tissues to lose more potassium than sodium. This disturbance increases the capacity of the tissues to retain water, hence the antidiuretic effect. Absence or lack of pituitary secretion allows the reverse phenomenon to occur. That is, potassium may accumulate to a greater extent than usual. This decreases the capacity of the

tissues to retain water, hence the diuresis and thirst of diabetes insipidus. It is not to be understood that sodium and potassium are necessarily the only elements involved. They are singled out because definite information extends to them only aside from a slight knowledge of the phosphorus, calcium and magnesium excretion.

"The diuretic effect of pituitary extract offers no point contrary to the hypothesis suggested. As a result of the necessity to excrete the potassium and sodium discharged into the blood there may be some competition between the tissues and kidney for water. In this case while the tissues are probably doing their best to retain water the kidney succeeds in obtaining enough to eliminate the salts brought to it. It must be remembered that the urine of pituitary diuresis is a concentrated urine with regard to its salt content. It contains as much as 1 per cent of chlorin, or three times as much as the blood serum of the dog.

"In conclusion it seems worth while to suggest that some of the pharmacological actions of pituitary extract may be due to alterations in the quantities or interrelationships of electrolytes in the tissues."

That posterior-lobe extract possesses a remarkable influence on the regulation of water metabolism in man and animals seems without dispute. Some investigators hold that, when used therapeutically, it exerts its influence in diminishing urinary output merely as an effective pharmacologic agent, in a manner analogous to the action of the members of the theobromin series in producing diuresis. Others, on the contrary, maintain that it exerts its effect through its action as a hormone. In discussing the functions of the posterior lobe of the pituitary Abel says, "One of these functions which is probably exercised continuously under normal conditions, but a diminished supply of which in the circulating blood leads to diabetes insipidus, manifestly has to do with the mechanism of water retention and transportation in the body."

Since 1912 when Frank first attracted attention to the relationship between the pituitary and diabetes insipidus in reporting his gun-shot case, and since 1913 when von den Velden and Farini directed attention to the antidiuretic action of extract of the posterior lobe, the literature has contained numerous reports of diabetes insipidus associated with pituitary tumors. The association of dystrophia adiposogenitalis and diabetes insipidus or polyuria has been several times recorded. It is not surprising, therefore, that the view that diabetes insipidus is due to disturbed function of the posterior lobe of the pituitary has been the one that has chiefly prevailed during the intervening years, especially when we consider that extract of this lobe is the most effective remedy we possess for the relief of the polyuria at the present time. An argument advanced against this conception, however, exists in the fact that many tumors of the pituitary have been reported in which the

symptom-complex of diabetes insipidus was absent. Acromegaly without diabetes insipidus, for instance, is very common. Abel, who supports the pituitary conception, has found that he has been able to isolate his pituitary tartrate, although in small quantities, from the tissues of the hypothalamic region, and offers the suggestion that when diabetes insipidus is not present in destructive pituitary tumors, there may be sufficient of the extract present in the hypothalamus to maintain normal water metabolism in the individual.

Although, since 1912, the view that diabetes insipidus is a result of disturbed function of the posterior lobe of the pituitary gland, dependent usually on the effects of a pituitary tumor, has been the one most generally supported, yet there are many investigators who contend that no direct relationship between the two exists. The opponents of this conception are those, who, on experimental and clinical grounds, believe that diabetes insipidus is purely of nervous origin and dependent upon lesions involving one or more structures comprising the hypothalamus.

Before presenting this evidence, a brief statement of the anatomical relationship of the hypothalamus and hypophysis may be instructive. The hypothalamus occupies the base of the brain immediately above the hypophysis and its infundibular stalk. It includes the subthalamie tegmental region and the structures forming the greater part of the floor of the third ventricle, viz., the corpora mammillaria, tuber cinereum, optic chiasma, and infundibulum.

The *corpora mammillaria* are two round white masses, each about the size of a small pea, and situated posterior to the infundibulum, and placed side by side below the gray substance of the floor of the third ventricle.

The *optic chiasma* is a flattened, somewhat quadralateral band of fibers, situated at the anterior part of the hypothalamic region at the junction of the floor and anterior walls of the third ventricle. It is in front and above the infundibulum.

The *tuber cinereum* is a hollow eminence of gray substance between the corpora mammillaria behind and the optic chiasma in front.

From the under surface of the tuber cinereum a hollow conical process, the *infundibulum*, projects downward and forward and is attached to the posterior lobe of the hypophysis by the infundibular stalk.

The extent of the brain substance comprising the hypothalamus is comparatively limited, and its close relationship to the pituitary explains how easily pituitary tumors gradually increasing in size and destroying the anterior and posterior clinoid processes of the sella could readily invade or compress the structures comprising it. The fact that the optic chiasma is a constituent part of the hypothalamus accounts for the occurrence of the bitemporal hemianopsia so frequently reported in diabetes insipidus accompanied by basilar tumors, gummata, or basilar luetic meningitis.

Erdheim,<sup>15</sup> a pathologist, of Vienna, writing in 1904 appears to have been the first to suggest on clinical grounds that the polyurias associated with organic brain lesions were actually dependent upon tumors involving the hypothalamus. It has been shown above that the pituitary conception of the origin of diabetes insipidus dates essentially from the year 1912, although Cushing had drawn attention to the polyurias in experimental hypophysectomies in 1910. As a result of experimental investigations doubt was very soon expressed concerning the pituitary origin of the disease, and evidence was advanced pointing to its being of nervous origin and dependent upon lesions in the hypothalamus just above the pituitary.

Camus and Roussy<sup>16</sup> were the first to investigate this problem experimentally. In 1913 they reported to the Société de Biologie that they had been able to produce transitory polyuria by puncturing the hypothalamus of dogs through the sphenoidal bone with a heated drill. In one dog a permanent polyuria and in addition adiposogenital dystrophy had resulted. Their report stated that the lesion lay in front of the infundibulum and involved the tuber cinereum.

These investigators continued their experiments<sup>17</sup> and in 1920 reported what seemed very conclusive evidence that the polyuria does not depend on a lesion of the pituitary by producing it in a dog from which the gland had been previously removed. Following the removal of the pituitary there was a transitory polyuria. More than a month later, after the polyuria had subsided, a second polyuria of equal intensity was produced by puncture of the tuber cinereum.

Aschner,<sup>18</sup> writing in 1916, obtained similar results to those of Camus' and Roussy's early researches and even claimed priority in these experiments. Confirmation was reported by Houssay and Hug,<sup>19</sup> in 1921.

Bailey and Bremer,<sup>20</sup> in 1921, reported from Cushing's Clinic a very careful piece of experimental work on dogs confirming the views of Camus and Roussy. With the technique used by the latter there was always risk of injury to the pituitary. By a special surgical technique Bailey and Bremer exposed the hypothalamus by the temporal route, which permitted an exposure of the whole region. The punctures of the hypothalamus could be made where desired, and the pituitary, being in plain view, could be carefully avoided. When the animals died or were sacrificed sections were made of the injured hypothalamus, and of the pituitary to make sure that the latter had not been damaged in the operation. In all of their thirteen dogs in which the hypothalamic puncture was performed there developed a polyuria which appeared in the first two days. According to the extent of the lesion it varied from a transient one, lasting from six to eight days, to an apparently permanent polyuria. It is interesting to note that in some of the dogs the physical effect of the puncture on the animals resembled that

following hypophysectomy. Lesions of the tuber cinereum produced in two dogs a cachexia hypophyseopriva with acute genital atrophy, and in two other dogs an insidiously developing adiposogenital dystrophy. The integrity of the pituitary was in each of these cases verified histologically. It is important to note that these researches confirmed the observations of Camus and Roussy to the effect that injury to the hypothalamus, in addition to causing polyuria, also, in some instances, resulted in the production of an adiposogenital syndrome, which has been supposed to be dependent on pituitary disturbance.

The experiments of Camus and Roussy and of Bailey and Bremer have been substantiated by Hanchett,<sup>21</sup> Curtis<sup>22</sup> and others.

Camus and Roussy hold that the tuber cinereum is the anatomic structure in the hypothalamus injury of which produces the polyuria. The experimental work of Helen Bourquin<sup>23</sup> would seem to indicate that polyuria can be induced by injuries of the corpora mammillaria, which she considers the site of the effective lesion causing polyuria. Dogs were used in the experiments and the injury to the mammillary bodies was induced by cauterizing them with an electric needle. She holds that it is an irritative phenomenon because the polyuria results from slight injury of the bodies, rather than by destruction, in which case it is not induced. She believes that the diuresis must be due to a substance produced in the mammillary bodies as a result of their irritation and which acts directly or indirectly as a diuretic. She failed to produce polyuria in dogs by removal of the hypophysis, but these same dogs developed a polyuria when their corpora mammillaria were irritated. As a result of her experiments she believes that the thirst of diabetes insipidus is secondary to the diuresis, for the diuresis develops in operated animals restricted to their average pre-operative water intake and quickly produces manifestations of desiccation in diabetic animals deprived of water. She is of the opinion that neither the autonomic nor somatic nervous system is concerned in the diuresis, for in her experimental dogs it ran its typical course after transection of the spinal cord at the level of the eighth cervical vertebra.

The experimental evidence, therefore, seems very conclusive that injuries to both the tuber cinereum and the corpora mammillaria in the hypothalamic region can cause a definite polyuria in dogs; that many experimenters have removed the posterior lobe of the pituitary without more than a transitory polyuria resulting; and that polyuria does occur in these hypophysectomized dogs when either the tuber cinereum or corpora mammillaria are injured or irritated.

In addition to this experimental evidence of the relationship between polyuria and lesions of the hypothalamus, a limited amount of clinical evidence has also accumulated in recent years. Fink<sup>24</sup> has collected from the literature 107 necropsies in cases of diabetes insipidus. In looking over the synopses of these cases it is interesting

to note that many of those showing disease of the pituitary also refer to associated involvement of some of the structures of the hypothalamus. The number of cases in which the lesion appeared to have been limited to the hypothalamus seemed very small. In fact, the writer could discover only 3. One of these is the often quoted case of Lhermitte,<sup>25</sup> published in 1922, in which a syphilitic lesion involved both the infundibulum and tuber cinereum. Babonniex and Lhermitte,<sup>26</sup> in 1925, reported another case of diabetes insipidus with syphilitic basilar meningitis and lesions in the infundibulum and tuber cinereum. Verron<sup>27</sup> reported a case following trauma in which there was a circumscribed necrosis of the infundibulum.

Since the appearance of Fink's paper, a case of diabetes insipidus was reported in 1928 by Elmer, Kedzierski and Scheps<sup>28</sup> in a patient who had a hypernephroma of the kidney with a metastasis in the hypothalamus. An embolus of malignant cells had blocked an artery causing a necrosis of the tuber cinereum. There was a pin-head sized adenoma in the anterior lobe of the hypophysis, which they considered had no bearing on the cause of the diabetes insipidus.

The comparative rarity of clean-cut cases of tumors of the hypothalamus without any evidences of involvement of the pituitary gland seems to justify the reporting of the following case:

**Case Report.**—O. H. (History No. 44676), male, married, a chauffeur, aged forty-three years, was admitted to the Church Home and Infirmary, November 9, 1927, complaining of intense pain in the lower part of the back and down the thighs, intense thirst and passage of enormous quantities of urine.

The family history was unimportant.

There was nothing of special importance in his previous history excepting that at twenty years of age he had contracted gonorrhea and that nine years ago he had had an attack of lumbago. He stated that his health had always been good up to the onset of his present illness. He had been employed as a chauffeur for several years.

The onset of his present illness began six months before admission, when he began to have some cough. In the last week of August he developed night sweats. On September 11 he had a slight pulmonary hemorrhage. The physician of the large corporation for which he worked, suspecting pulmonary tuberculosis, arranged for his admission to the State Tuberculosis Sanitarium, at Sabillasville, Maryland, where he remained for about nine weeks previous to his admission to the Church Home and Infirmary. Two weeks previous to his admission to the latter institution he began to have severe pains in the lumbar region and down the outer aspect of the thighs. About this time he also developed intense thirst and marked polyuria. Although the patient was thought to have tuberculosis at the sanitarium, no tubercle bacilli were ever found in his sputum. Recently he had noticed a projecting lump over the left temporal region of the skull. He had lost 30 pounds in the last six months. The pain in the back became so intense that Dr. V. F. Cullen, Superintendent of the sanitarium, advised the patient to return to Baltimore to consult Dr. G. E. Bennett to see if there were any orthopedic condition producing the lumbar and thigh pains. He left the sanitarium the morning of November 9 and on the train journey to Baltimore became delirious and very confused as to time and place.

When he arrived in Baltimore he had high fever, and, as his condition seemed so serious the company physician arranged for his admission to the hospital the same afternoon. When Dr. Bennett saw him he realized that the condition was not essentially an orthopedic one and asked the writer to see the patient in consultation.

*Physical Examination.* The patient was seen on November 10, 1927, the day after admission. The following is a brief summary of the detailed note made at that time. The patient was complaining of intense pain in the lumbar region and down the thighs and took several long draughts of water during the examination. Moderately nourished. No special anemia or cyanosis. No jaundice.

*Cranium.* There was a prominence 4 cm. in diameter over the left fronto-temporal region with a crater-like edge.

*Eyes.* No hyperthyroid features. Pupils unequal, the left being larger than the right. Scarcely any reaction to light but ready response to accommodation.

*Pulse.* Essentially normal. No palpable sclerosis.

*Thorax.* Diminished expansion throughout the entire right side. Lower intercostal spaces partially filled out.

*Lungs: Right.* Tactile fremitus diminished below the third rib in front and throughout the entire axillary region. Over this area there was marked dullness on percussion and increased resistance. The breath sounds were enfeebled and nowhere tubular. The voice sounds were enfeebled. No râles. Posteriorly, the tactile fremitus was exaggerated over the supraspinous fossa, diminished over the lower interscapular and absent over the subscapular area. There was marked dullness throughout with increased resistance. The breath sounds were markedly enfeebled throughout but nowhere tubular. There were a few medium moist râles over the supraspinous fossa. The vocal resonance was a little exaggerated above but almost absent below.

*Left.* Percussion and auscultation were essentially normal, excepting for a few moist râles at the base.

*Heart.* Sounds clear. By percussion the left border reached the mammillary line. There was no recognizable dullness over the manubrium.

*Abdomen.* No ascites. The liver dullness extended 3.5 cm. below the costal margin. Border not felt. No nodules felt on the surface. Spleen not felt. No masses elsewhere in abdomen.

There was no edema of the shins or feet.

*Deep Reflexes.* All were considerably exaggerated.

*Superficial Reflexes.* Normal.

*Joints.* No arthritis in joints of extremities.

*Spine.* In getting patient to sit up great pain in the lumbar region was experienced. The lumbar spine was almost immobile. There was no kyphosis or scoliosis.

*Glandular System.* No general glandular enlargement.

*Impression.* The following preliminary diagnosis was made at the time:

1. Examination of the chest, to be supplemented by Roentgen ray studies, without heart being displaced to the left suggests strongly tumor of the right lung and pleura.

2. Tuberculosis of lung and pleura to be excluded, but does not seem probable.

3. Tumor over left temporal bone suggests strongly a malignant metastasis, although a gumma has to be considered, as patient has anisocoria and a suggestive Argyll-Robertson pupil.

4. Has diabetes insipidus, which suggests pituitary involvement due to a metastasis or gumma. Involvement of the hypothalamic region might

produce the polyuria and polydipsia. Has passed 8170 cc. in less than twenty-four hours since admission.

*Subsequent Studies and Course.* The fluid intake and urinary output were daily measured until patient's death on November 28, 1927. The urine was extremely pale, the specific gravity averaging 1.004. There was no albumin or sugar. Microscopically a few red blood and pus cells were noted. The highest urinary output was 10,940 cc. on November 13, and the highest fluid intake was 12,000 cc. on November 18. On November 13, when the urine output was 10,940 cc. surgical pituitrin, hypodermatically, was started. On November 14, the pituitrin injections were increased to twice daily and November 16 the urine had fallen to 5150 cc. Curiously enough on November 18 the urine rose to 9375 cc. and the fluid intake to 12,000 cc. Owing to this increase 1 cc. of pituitrin three times daily was ordered on November 19 and on this day the urine fell to 5500 cc. and the fluid intake to 7000 cc. On November 22 the urine and fluid measurements were respectively 4500 cc. and 5200 cc. The last dose of pituitrin was given on this date. From this date on there were further diminutions in output and intake but it was not possible to keep careful records as the patient was quite delirious and in a semistupor at times. For the twenty-four hours of November 27, the day before his death, the output was recorded as 1100 cc. and intake 2000 cc. The patient was delirious and in a semi-coma for the last four days preceding his death, which occurred on November 28.

The blood count on November 10 was as follows: red blood cells 3,310,000; white blood cells, 11,040; hemoglobin not recorded. Differential count was essentially normal.

The blood Wassermann test was negative. A Roentgen ray of the cranium showed that the sella was of normal size and shape. There was also a defect in the left temporal bone at the site of the swelling. The Roentgen ray of the chest showed a dense shadow involving the whole of the right lung. A biopsy was done on the tumor over the left temporal region for purposes of diagnosis. The sections were studied by Dr. Fried, the hospital pathologist, who reported that the tumor was an alveolar carcinoma.

*Autopsy.* The autopsy was performed by Dr. Fried, the writer being present. Following is a brief summary: The right lung was completely involved by the cancer with metastases to the mediastinal and peribronchial glands. There were also metastases present in the liver, pancreas, the left temporal bone and brain.

Our interest, naturally, was centered in the brain findings. On opening the skull there was found a defect in the left temporal bone due to a tumor metastasis. The tumor had grown out under the left temporal muscle and extended inward causing compression, but not actual involvement of the left frontal lobe. There were no other nodules seen anywhere on the surface of the brain.

The base of the brain was very carefully studied *in situ*. There was absolutely no evidence of any tumor mass seen on the surface of the brain in the infundibular region. The pituitary body was normal in size and showed absolutely no evidence of metastatic involvement.

The brain was hardened before being sectioned. It was found that a tumor 3 cm. in diameter was present in the hypothalamus involving the infundibulum and tuber cinereum. It was not visible from the outside. There was no bulging at the base and there was no evidence of compression of the infundibular stalk. The tumor began immediately beneath the pia at the attachment of the infundibular stalk and extended upward into the substance of the hypothalamus a distance of 3 cm. There was also a metastatic nodule about 1 cm. in diameter in the pons.

The histologic examination of the primary lung tumor, which probably began in a bronchus, as well as of the metastatic tumors of the hypothalamus and elsewhere showed it to be due to an alveolar carcinoma.



**Discussion.** From an anatomical standpoint the above case would appear to be a clear-cut instance in which the classical symptoms of diabetes insipidus were brought about by the development of a metastatic hypothalamic tumor secondary to a primary alveolar carcinoma of the lung, without any evidence of involvement or compression of the posterior lobe of the pituitary. The case would seem to be a strong argument against the view that diabetes insipidus is dependent upon the absence of the diuretic-antidiuretic pituitary hormone, since the presumption is that the formation of this hormone was not interfered with. There is now abundant experimental proof that the pituitary can be removed in dogs without diabetes insipidus developing, and it is believed that the polyurias resulting from the hypophysectomies in early experimental work were due to a concomitant injury of the structures in the hypothalamus. We have seen also that experimental injuries to the tuber cinereum and corpora mammillaria in dogs can be produced even in hypophysectomized dogs in which polyuria failed to develop after the pituitary was removed. It is contended by many that in those cases of diabetes insipidus reported as being dependent upon hypophysial disease there is also an associated injury of the hypothalamic tissue, and many of the case reports would seem to bear out this contention. How experimental lesions or tumors of the hypothalamus cause the diuresis is still an unsolved problem. While those supporting the hypothalamus origin of diabetes insipidus contend that the disease is of nervous origin, Bailey and Bremer believe that it is not dependent upon a supposed nervous or vascular regulation of the kidney. They found that it may be induced in animals whose kidneys have previously been denervated and, when present, persists after kidney denervation has been performed. Bourquin also found that neither the somatic nor autonomic nervous systems are concerned in the diuresis of experimental diabetes insipidus, as it runs its typical course after transection of the spinal cord at the level of the eighth cervical vertebra.

Do the structures in the hypothalamus contain a diuretic-antidiuretic hormone the prevention of the formation of which, as in the case of tumors in this region, leads to a disturbance of water metabolism and regulation? The investigations of Abel and his associates have shown that extracts of the infundibular region show this pituitary tartrate salt in small amount, and Abel advances the view that the failure of diabetes insipidus to develop in reported cases of pituitary disease may be due to the fact that there is sufficient of the diuretic-antidiuretic hormone in the hypothalamic tissues to prevent this symptom-complex from supervening. One can conceive that there might develop a compensatory increase in the production of this factor in the hypothalamus following earlier destruction of the function of the posterior lobe. The question has to be considered whether the pituitary tartrate, possessing diuretic-

antidiuretic properties, found in the hypothalamus by Abel is merely the secretion of the posterior lobe which is caught *en route* from the pituitary to the third ventricle, whence it eventually enters the circulation. Sato<sup>29</sup> in 1928 confirmed Abel's findings that the hypothalamus contains a substance which has an oxytocic action and also demonstrated the presence of a substance that possessed diuretic-antidiuretic properties similar to those of the posterior lobe of the hypophysis. He found that the whole of the tuber cinereum contains as much of the oxytocic and diuretic-antidiuretic substance as is contained in 1 to 2 or 2 to 4 mg. of the posterior lobe of the hypophysis. He believes that it exerts its effect through its hormonal action. It appears apparent to him that the diabetes insipidus that supervenes after destruction of the tuber cinereum is due to the fact that this diuretic-antidiuretic hormone is no longer formed.

It will be seen then that even though we may assume that lesions of the hypothalamus (tuber cinereum and corpora mammillaria) may cause diabetes insipidus, there are two views held by investigators as to how it is brought about. According to one view, the mechanism is through the nervous system—the nervous origin of the disease, but it is hard to explain the disease on this basis when it is found that it develops in experimental animals with lesions of the hypothalamus even after the kidneys have been denervated or after complete transection of the cervical cord. According to the other view it is due to the failure of the tuber cinereum or corpora mammillaria to produce a specific diuretic-antidiuretic hormone. The question should also be raised here as to whether tumors of the hypothalamus associated with diabetes insipidus may cause an interference of the transport of the diuretic-antidiuretic hormone from the posterior pituitary lobe to the third ventricle.

The possible interrelationship between the posterior lobe of the pituitary and the structures in the hypothalamus in connection with the etiology of diabetes insipidus is further complicated by the interesting fact that it now seems quite certain that these two structures are linked up by nerve fibers. Reference has already been made to the fact that Cajal and Cushing have demonstrated such fibers. An interesting observation has been made by Loewy<sup>30</sup> who destroyed the posterior lobe of the hypophysis in animals, and after from ten to fourteen days examined the tuber cinereum in serial sections. He found degeneration of the nucleus paraopticus and injured cells in the tuber cinereum (ganglion parahypophysios). The cells of these nuclei send out fibers which pass through the infundibulum to the posterior lobe of the hypophysis thus forming a united system, the injury of any portion of which, he believes may cause diabetes insipidus. Similar results were found by Clara Kary<sup>31</sup> who found axis cylinder fibers and only a few glia cells in the infundibulum. She observed that injury to the infundibulum led to degenerative changes in the tuber cinereum.

In this connection, it is interesting to note that Cushing, in his Cameron Lecture of 1925, reported that by shrinking the brain by the Weed method and compressing the hypophysial stalk by placing a silver "clip" about it he was able in dogs to produce the same train of symptoms as were evoked by Bailey and Bremer in their experiments on the hypothalamus, viz., a prolonged polyuria with subsequent tendency to adiposity.

A recent research of Trendelenburg,<sup>32</sup> of Freiburg, in 1928, seems of the greatest importance in pointing toward a compensatory inter-relationship between the posterior lobe of the pituitary and the tuber cinereum of the hypothalamic region. In his experiments on dogs he found that in the hypophysectomized animals there appeared in the tuber cinereum an increasing amount of an antidiuretic substance, which acts exactly as does the secretion of the posterior lobe of the pituitary, and which is present in the tuber cinereum of normal dogs in much smaller amounts. He finds that this also applies to the oxytocic effect. He believes that diabetes insipidus, at least in animals, is probably purely hormonal in origin, and that when the diuretic-antidiuretic hormone of the posterior lobe of the hypophysis is destroyed by disease there appears a vicarious assumption of function on the part of the tuber cinereum in producing this hormone, and that the diabetes insipidus only supervenes in hypophysectomized animals when the tuber cinereum is destroyed. In his opinion this theory satisfactorily explains the previously conflicting views held concerning the explanation of experimental diabetes insipidus in dogs.

Elmer, Kedzierski, and Scheps, who reported the case of diabetes insipidus, due to an embolic hypernephroma metastasis, causing necrosis of the tuber cinereum already referred to, give an interesting classification of diabetes insipidus from an etiologic standpoint based on the experimental, clinical and pathologic experience at the present time. The classification would appear to clear up many of the conflicting views concerning the disease in human individuals. Their classification is as follows:

(a) Cases due to destruction of the posterior lobe of the hypophysis. Here the posterior lobe extract fails entirely or only in part to sensitize the regulating centers for water and salt in the hypothalamus. In these cases pituitrin has a definite, though transitory, therapeutic effect, because the regulatory centers in the hypothalamus are intact.

(b) Cases due to destruction of the water- and salt-regulating centers in the hypothalamus. In these cases the secretion of the posterior lobe is still produced, but it cannot sensitize the hypothalamic centers because they are destroyed. In this group the pituitrin has no effect whatever, since the regulating centers in the hypothalamus are destroyed and are incapable of sensitization.

(c) Cases in which there is an interruption of the communicating

nerve fibers connecting the hypothalamus (tuber cinereum) and the posterior lobe of the hypophysis. This group, they state, is insufficiently understood and requires further investigation. The therapeutic effect of pituitrin is not stated in this group.

The authors believed that their case belonged to the second group. The case here reported would seem to fall in the same group, although there did seem to be a therapeutic response to pituitrin. They emphasize that all cases do not fall accurately into their three groups, since there may be several factors at work in individual cases.

It will be seen that there are very conflicting views concerning the etiology of diabetes insipidus. The case reported in this paper definitely belongs to the group in which the pathologic lesion is present in the hypothalamus without evidence of any organic disease of the pituitary. The fact that the tissues of the hypothalamus, particularly of the infundibulum and tuber cinereum, were involved, is significant in our own case, but it is difficult to understand how diabetes insipidus occurred with an intact posterior lobe of the pituitary unless the transport of its secretion was interfered with in its passage to the third ventricle. On the view that water metabolism is regulated by centers in the hypothalamus controlling water metabolism and salt excretion an explanation could be found, but the analysis of the literature, and the effect of pituitrin therapeutically in many cases, forces the writer to the conclusion that water metabolism is regulated by hormonal control, whether that hormone be produced in the posterior lobe of the pituitary or in the tuber cinereum or mammillary bodies.

The demonstration of nerve fibers connecting the tuber cinereum and the posterior lobe of the pituitary is rather significant and further complicates the problem from the standpoint of etiology. The possibility of the interruption of nervous impulse along these fibers has at least to be entertained as a factor in the etiology of diabetes insipidus. It is interesting in this connection to quote from a personal communication from Harvey Cushing dated September 10, 1928, in reply to a request as to his present views concerning the etiology of diabetes insipidus. "I am sending you a copy of my Cameron Lectures in which I ventilated myself on the subject to try and reconcile Bailey's and my somewhat divergent views. There is of course no question but that the centers lie in the hypothalamic region since nerves appear to descend and get lost in the pars nervosa. We see a lot of diabetes insipidus, a good deal of it post-operative, because we are dealing fairly often with suprasellar tumors in these days and there is no question but that the water metabolism upset comes from damage of the third ventricle."

**Summary.** 1. A case of diabetes insipidus due to an alveolar carcinoma of the hypothalamus, secondary to a primary carcinoma of the lung, and without an involvement of the pituitary, is reported.

2. The case would naturally tend to support the view held by many that the diabetes insipidus is due to disturbance of certain regulatory centers in the hypothalamus.

3. The studies supporting the pituitary and hypothalamic conception of the origin of the disease is reviewed.

4. Reference is made to the fact that it now seems amply demonstrated that there are definite nerve fibers connecting the tuber cinereum and the posterior lobe of the hypophysis.

5. The belief is expressed that, although there may be certain centers in the hypothalamus regulating water exchange in the body, the evidence seems very strong that disturbance of the action of a diuretic-antidiuretic hormone produced in the posterior lobe of the pituitary is a very important factor in the etiology of the disease, possibly by sensitizing these centers or by influencing their function.

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## MIKULICZ'S DISEASE AND THE MIKULICZ SYNDROME.

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IN 1888, Mikulicz<sup>1</sup> discussed before a German medical society a case of the condition which has since been called by his name; and in a later publication<sup>2</sup> reported it in fuller detail. Even before this, there had been a few similar instances recorded and since then there have been many contributions and collections of reported cases made. Lane<sup>3</sup> estimates that from 1888 to 1922 more than 120 articles had been published on the subject. Not only the disease proper, as described by Mikulicz, has been discussed, but allied affections of the salivary and lachrymal glands have been studied, very similar in many clinical manifestations but perhaps of different etiology. To all these latter the title Mikulicz's syndrome may well be applied; or, if desired, this term may include all diseases showing the peculiar involvement of the lachrymal and salivary glands which have been under consideration.

Yet all these conditions are still of uncommon enough occurrence to warrant the report of two additional cases, one of them apparently a genuine instance of the condition originally described by Mikulicz, the other of an entirely different pathological nature, being a manifestation of leukemia, but simulating the first case clinically in many important particulars. The study of Mikulicz's disease proper is of especial interest as bearing upon the possible influence of tuberculosis in producing the symptoms.

**Case Reports.** CASE I.—Mabel J., aged nine years when admitted to the Children's Hospital of Philadelphia, April 25, 1924. Her previous health had been good except for the occurrence of measles and occasional colds. A little over six months before admission the upper lids of both eyes had become swollen and had remained so. About a week later swelling developed in the region of both parotid glands. She continued to feel well and to play about in her usual good condition. There had been no pain and no disturbance of the lachrymal or the salivary secretion.

**Condition in the Hospital.** She was a well-developed mulatto girl. The upper eye-lids seemed swollen, but on everting the lids this appearance was found due to a hard, lobulated, red mass, about 1 to 1½ cm. long, attached on the outer portion to the upper lid. The tonsils were only slightly enlarged. Swelling over both parotid regions extended downward to shortly below the angle of the jaw and backward to a little behind the lobes of the ears. The swelling was not movable or tender, and there was no pain on opening the mouth. There was some enlargement of the glands beneath the body of the jaw, probably due to involvement of the submaxillary salivary glands. The cervical lymphatic glands did not seem to be affected. There was a small gland in the left axilla and one in each groin. The liver did not appear to be enlarged. The spleen could not be felt distinctly. The Roentgen ray examination of the chest and skull (Dr. Ralph Bromer) did not

indicate the existence of any pathological condition. The Wassermann test was negative, as was the examination of the urine and the cutaneous and intracutaneous tests for the presence of tuberculosis. Studies of the blood on several occasions gave the following results:

TABLE I.—BLOOD PICTURE OF CASE.

	R.B.C.	Hgb.	Lets.	Neu-troph.	Lymph.	Large mono.	Trans.	Eosin.	Basoph.
April 26	5,160,000	77	5700	43	49	3	3	1	1
May 22	.....	..	7100	42	44	1	2	10	1
June 14	.....	..	7900	69	19	2	7	3	

The child was removed from the hospital on August 27, 1924. The accompanying photograph (Fig. 1) gives a good picture of her appearance. While in the hospital the patient received systematic Roentgen ray exposure of the parotid glands, but without noticeable effect. On June 3, a considerable portion of the left lachrymal gland was removed and studied histologically.

**Histological Report** (Dr. A. Waltz): "Sections made from the lachrymal gland show a marked alteration of the glandular structure. There are comparatively broad bands of fibrous tissue dividing the gland into irregular but distinct lobules. These lobules for the most part contain single or conglomerate tubercles, which show the typical central area of epithelioid cells, with numerous giant cells surrounded by a zone of small round cells, but practically without necrotic areas. A few of the lobules contain remnants of glandular elements and large numbers of small round cells.

"The process is typical of tuberculosis, except that with such a general involvement of the gland one would expect more necrotic material and probably less fibrosis. However, no tubercle bacilli could be found by special staining methods, neither could tuberculosis be produced in guinea pigs by subcutaneous inoculation with glandular tissue" (Fig. 2).

This case may be called a typical instance of Mikulicz's disease proper, not dependent upon leukemia or any other condition of the blood, and without positive evidence of the existence of tuberculosis. The relationship to this latter disease will be referred to again.

**CASE II.**—Carolyn R., aged eight years, referred to me by Dr. Pursell of Phillipsburg, N. J., was admitted to the Children's Ward of the Hospital of the University of Pennsylvania, April 2, 1922. The child developed symptoms of Friedreich's ataxia when about two years of age. This condition very gradually grew worse, but gave little trouble until four or five months before admission. About this time swelling appeared in the "glands of the neck" together with some irregular fever. She had been growing thin and weak. Two months before admission a great enlargement of the spleen was discovered by Dr. Pursell, who had been called in on account of a severe febrile attack. On admission to the hospital, the child looked and seemed ill. There were the usual symptoms of Friedreich's ataxia, which need not be detailed. The upper eye-lids appeared swollen, and the parotid glands were large and hard. The cervical and submaxillary lymphatic glands were enlarged and somewhat matted. Radiographic examination showed some evidence of involvement of the mediastinal glands. The spleen was much enlarged and hard, extending to the right



FIG. 1.—Mabel J. Showing the enlargement of the lachrymal and parotid glands.

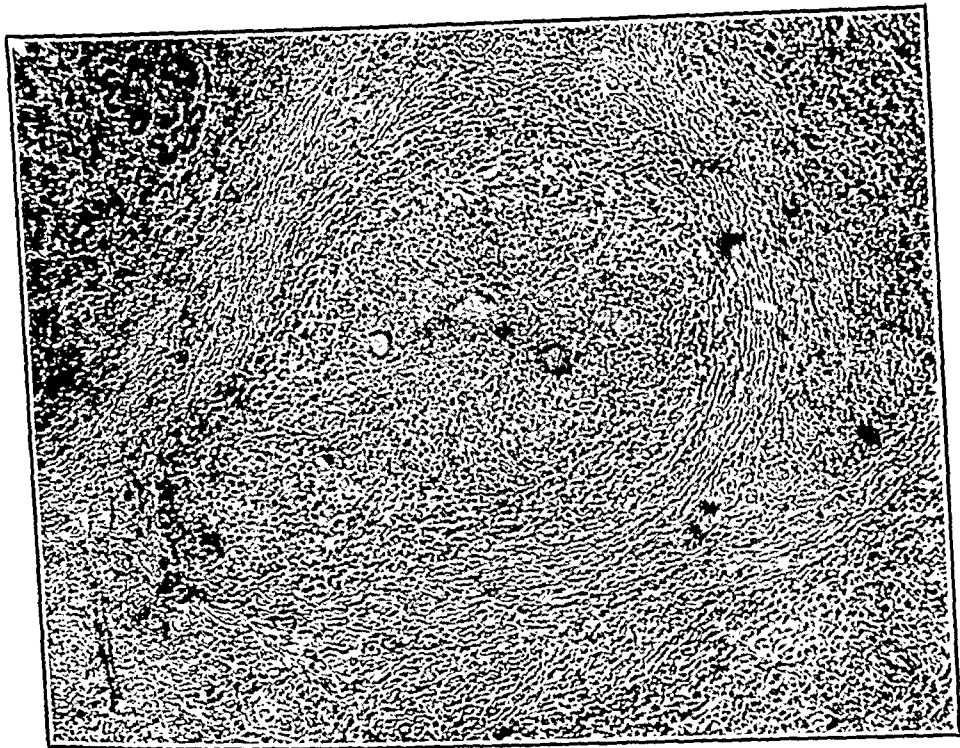


FIG. 2.—Photomicrograph (Case I) with central portion showing a typical tubercle histologically. Collection of epithelioid and giant cells with the usual areola of small round cells. Broad fibrous bands separate this tubercle from the rest of the section, giving a lobular appearance. The upper left area shows remnants of glandular elements and infiltration with numerous small round cells.





FIG. 3.—Case II, Carolyn R. Mikulicz's syndrome dependent upon leukemia.

of the median line three fingers' breadth below the costal margin. Several small purpuric spots were found on the left calf. The urine exhibited a trace of albumin. Another examination of the child a little later made it evident that the apparent swelling of the eye-lids was due to enlargement of the lachrymal glands on each side. Repeated examinations of the blood were made with the following results:

TABLE II.—BLOOD PICTURE OF CASE II.

	R.B.C.	Hgb.	Lcts.	Polys.	Mononuc.	Trans.	Lymph.	
April 22	2,080,000	42	340,000	2.0	3	0	95.0	Some anisocytosis. No nucleated redds. No myelocytes; most of the lymphocytes a little larger than usual but not sufficiently to determine from a laboratory point of view whether the case is of the acute or chronic type. (Dr. Cope.)
May 1	1,780,000	37	190,000	4.0	1	0	94.0	1 myelocyte, 1 normoblast in 20 w.b.c.
May 10	1,220,000	25	757,000	8.0	3	1	87.0	1 myelocyte; no nucleated red cells.
May 17	1,100,000	17	600,000	3.5	2	0	94.5	1 myelocyte, 1 nucleated red in 20.

The patient was removed from the hospital May 24, against advice, and died on the following day. While in the hospital, she had frequent nose-bleeds. The eye-ground of the right eye exhibited many hemorrhages. Roentgen ray treatment of the bones of the body was systematically applied, but without benefit. The temperature ran an irregular febrile course. The accompanying photograph (Fig. 3) gives a good illustration of the appearance of the patient.

No autopsy was obtained in this case, yet even without this the diagnosis is clearly indicative of involvement of the parotid and lachrymal glands as a part of a general lymphocytic leukemia.

**Comment.** In view of the numerous valuable critical studies of the subject that have appeared in the years since Mikulicz made his contribution, no extensive review of the literature will be attempted. For further information regarding it one may consult the published papers of, among others, Howard,<sup>4</sup> Thursfield,<sup>5</sup> Igersheimer and Pöllot,<sup>6</sup> Hochschild,<sup>7</sup> Marsh,<sup>8</sup> Schaffer and Jacobsen,<sup>9</sup> Hamburger and Schaffer.<sup>10</sup> A brief synopsis of what is known of the disease may not be amiss.

The disorder as described by Mikulicz consists of a chronic symmetrical enlargement of the lachrymal and salivary glands, beginning in the lachrymal glands and perhaps limited to them, but usually gradually extending. The swelling is hard, painless and apparently noninflammatory. There is no disturbance of the lachrymal or salivary secretion and the general health is not affected. The author emphasized the nonparticipation of the lymphatic glands in the process, and the lack of alteration of the blood. He could discover no cause for the condition, but believed it was an

infection of some sort. Pathologic study of a portion of the lachrymal gland which had been removed revealed a widespread infiltration with round cells suggesting lymphadenomatous tissue.

Later experience of other investigators has shown that there is a number of other conditions with clinical manifestations in the lachrymal and salivary glands like those of Mikulicz's disease proper but with differences in other respects. It does not seem reasonable to base a sharp distinction on the existence, or lack of it, of moderate enlargement of some of the lymphatic glands; first, because the pathological process in the diseased salivary glands may well have its origin in some of the small lymphoid nodules which are naturally present, and consequently involvement of the lymphatic tissue elsewhere might well be expected; and, second, because moderate enlargement of the lymphatic glands in different parts of the body is of such common occurrence that its association with the salivary disorder may easily be merely a coincidental one.

Regarding the pathologic anatomy of the affected glands in Mikulicz's disease it has been found that there is a great lack of uniformity in the histologic changes which occur. This will be referred to later. Further, it has been claimed by Howard and others that there are a whole series of cases which form links from one variety of disorder of the salivary glands to other much more widespread infections, such as leukemia. This does not, however, appear to be definitely proven, and Schaffer and Jacobsen contend that it is not the case.

It is evident, then, that the relationship of the different forms of Mikulicz's syndrome to each other, the etiology, and the pathologic anatomy are far from being entirely clear. Nevertheless for the purpose of study some classification is needed. There have been a number of attempts at this. Howard has divided the syndrome into Mikulicz's disease proper, pseudoleukemia and leukemia. Thursfield's classification is rather more elaborate. That of Schaffer and Jacobsen, based upon the latter, is probably as convenient as any. These last authors divide the syndrome into:

1. MIKULICZ'S DISEASE.

- (a) Familial.

- (b) Mikulicz's disease proper.

2. MIKULICZ'S SYNDROME.

- (a) Leukemia.

- (b) Tuberculosis.

- (c) Syphilis (?).

- (d) Lymphosarcoma.

- (e) Toxic.

1. Lead.

2. Iodids, etc.

- (f) Gout.

- (g) Febris uveoparotidea subchronica.

There are in addition some acute and some relapsing forms to which no reference is made here.

As concerns the various forms mentioned, the first is a congenital familial affection very rarely seen. Quinke<sup>11</sup> made a brief reference to a family in which several cases had been observed, and Léri and Gutmann<sup>12</sup> reported another instance of familial occurrence. The symptoms are those of the ordinary disease. A case said to be of this nature is reported by Laffolley<sup>13</sup> but it is doubtful whether it properly belongs in this category.

Mikulicz's disease proper is that as originally described by Mikulicz, the cause of which is unknown. My first case is a very typical instance of this. The symptoms have already been mentioned. As stated earlier it does not seem necessary to exclude all cases in which there is some moderate enlargement of the lymphatic glands.

Considering the Mikulicz syndrome, as apart from the forms already mentioned, that due to leukemia is well illustrated in my second case. In this form the involvement of the salivary and lachrymal glands is only one manifestation of the general leukemic process. It is, however, distinctly a rare one.

The influence of tuberculosis has been much discussed. A valuable contribution upon the subject was that of Igersheimer and Pöllot, who published the report of a case of enlargement of the lachrymal and submaxillary salivary glands. The histologic examination of the lachrymal glands showed a round-celled infiltration, small nodules of epithelioid cells and numerous giant cells, with an overgrowth of connective tissue, producing an appearance, which, they say, would, without hesitation, have been diagnosed as tuberculosis. There were, however, no tubercle bacilli found, repeated subcutaneous injections of the patient with tuberculin gave negative results and the introduction of portions of the excised gland into the anterior chamber of the eye of two rabbits and into the peritoneal cavity of two guinea pigs was entirely without result. The authors then enter upon a careful, thorough and critical discussion of the problem. In view of the importance of the subject this may well be reviewed here somewhat in detail. They raise the question whether cases of Mikulicz's disease with the histologic picture of tuberculosis are in reality tuberculous in spite of the absence of all positive proof of the existence of tubercle bacilli, or whether there exist other causes capable of developing an inflammatory condition which may produce a histologic picture resembling that of tuberculosis. To elucidate this they publish a valuable clinical review of all the reported cases, 44 in all, of enlargement of the lachrymal glands, with or without involvement of the parotids, which had been regarded by the reporters as possibly or certainly tuberculosis, or which had exhibited histologic changes of the glands resembling those seen in their own case and indicating a tuberculous lesion. Only 3 cases were found in which they could regard the

process as certainly tuberculous, and 2 others in which the diagnosis seemed probable. It may be said here that one of the 3 cases, that of Krailsheimer<sup>14</sup> is reported by the author as showing tubercles and giant cells, but no report is made of the finding of tubercle bacilli. A translation of this article<sup>15</sup> in an English journal apparently incorrectly says "tubercle bacilli" instead of "tubercles." This appears to have caused some confusion. The case cannot be regarded as a proven one of tuberculosis. Igersheimer and Pöllot conclude that tuberculosis has, as a rule, nothing to do with the production of Mikulicz's disease, although in some cases the tubercle bacillus is capable of producing the condition. They maintain, further, that the presence of epithelioid tubercles and of giant cells in the gland is no positive proof of the existence of tuberculosis there. The condition in my first case would seem to be entirely in support of this view. Thursfield, among others, also expresses the opinion that although tuberculosis can produce Mikulicz's disease the great majority of the cases have no connection with this cause. Bearing upon this conclusion especial attention might be called, for instance, to the case of van Duyse<sup>16</sup> in which epithelioid cells and typical giant cells were found in an excised portion of the lachrymal gland. The tumors, however, disappeared in six weeks under the administration of potassium iodid. A case of Fleischer<sup>17</sup> was very similar to this, bioscopic examination of the lachrymal gland strongly indicating tuberculosis. Baumgarten who examined the slides admitted the similarity to the histologic picture of tuberculosis, but stated that a positive diagnosis could be made only by animal inoculation or by the finding of the bacillus. The swelling in the glands in Fleischer's case disappeared entirely within three months. The case of Külbs<sup>18</sup> suggested tuberculosis in many particulars on histologic examination, although autopsy made some time later, after suicide, revealed no evidence of tuberculosis anywhere in the body. A much more recent review of the literature by Marsh failed to add any to the three instances of tuberculosis regarded by Igersheimer and Pöllot as certain. In Marsh's own patient the tumors were all of decided hardness, the tuberculin reaction was positive, miliary tubercles and epithelioid nodules with giant cells were discovered at the time of microscopic examination, but no tubercle bacilli were found and there was no caseation. No inoculation tests were made. Later the involved salivary glands resolved to a great degree. The patient was suspected of having pulmonary tuberculosis but this was never proven. In a patient reported by Scales<sup>19</sup> there was involvement of the lachrymal and parotid glands. The tuberculin test was negative. Microscopic studies of a removed lachrymal gland showed many tubercles, giant cells, and a round-celled infiltration; no necrosis or tubercle bacilli. Various pathologists examined the specimen with a diversity of opinions. Later the swelling of the remaining lachrymal gland

practically disappeared and there was a marked decrease in the size of the parotids.

The influence of syphilis is very uncertain. Some cases of Mikulicz's syndrome have improved under antisyphilitic treatment; but this is not definite proof that there were syphilitic. There may be an actual connection but it is not proven.

Sarcoma has repeatedly been described as involving salivary glands and the lymphatic glands as well.

Finally there is the curious condition described by Heerfordt<sup>20</sup> under the title of "Febris uveoparotidea subchronica," and later by a few other observers including Hamburger and Schaffer, in which iridocyclitis is the prominent symptom, associated with parotid enlargement and often with involvement of the other salivary glands, and of lymphatic glands as well, and in some cases attended by a polyneuritis. The relationships of this disorder are varied and obscure.

Regarding the influence of age, Mikulicz's patient was an adult. An analysis of Howard's series of 55 cases of Mikulicz's disease proper show that 7 were not over fifteen years of age, and of these 2 were not over six years. Taking Mikulicz's syndrome as a whole, including the 55 cases mentioned, there were 81, with 17 not over fifteen years of age, 6 of these being not over six years. I do not know that there has been any collective study of the age incidence since the date of Howard's contribution, but this is sufficient indication that although the syndrome is more commonly observed after childhood it is comparatively not infrequent during early life.

The cause of the enlargement in Mikulicz's disease proper is unknown. Thursfield suggests that it is probably dependent upon irritative processes in the pharynx, mouth and conjunctiva. In other forms of Mikulicz's syndrome it has to do with the original cause of the general condition.

In the matter of the pathologic anatomy of the disease, it would seem that the primary change in the glands consists of an extensive deposit of small round cells which more or less displace and often compress the glandular parenchyma. These cells may be an infiltration of leukocytes, or a proliferation of the nests of lymphadenoid tissue normally present in the glands. These changes are, however, not uniformly or solely seen, as already pointed out. Sometimes considerable new-formed connective tissue has been discovered, indicating a chronic inflammation, and in a comparatively large number of the cases in which histologic studies have been made a condition strongly suggesting the changes seen in tuberculosis has been found. By some observers giant cells, apparently genuine, have been described, and by others these formations have been designated as pseudo giant cells, or by other terms. There is rarely any evidence of caseation. The hardness of the gland, the tendency to decided connective tissue overgrowth, and the

absence of caseation are not in accord with the typical picture of tuberculosis, but in other respects the similarity is marked.

With regard to the prognosis and treatment, these depend upon the nature of the case. In the secondary cases, they are entirely that of the primary disease. It is noteworthy that even in such cases the treatment of the enlarged salivary glands by Roentgen ray or radium may at times reduce the swelling; but the general disease may go on to a fatal issue. In my own leukemic case Roentgen ray treatment was entirely without effect.

In the cases of Mikulicz's disease proper the prognosis is uncertain, but not entirely unfavorable. Thursfield states that "one to five years as a rule releases the patient" from the discomfort and disfigurement. Sometimes the swelling has disappeared during the occurrence of some general infection, to reappear later. The use of radium or Roentgen ray in treatment of the parotid swelling has had remarkably good results in some instances, and in others the enlargement has entirely or largely vanished without satisfactory cause being known. In my own case Roentgen ray treatment was without benefit. Surgical removal of the enlarged lachrymal glands has been done repeatedly, and with good results in relieving the interference with vision and the disfigurement.

**Summary.** Two cases of Mikulicz's syndrome are reported; one dependent upon leukemia, the other, which might be called Mikulicz's disease proper, having no discoverable cause. The symptoms and lesions are discussed with special reference to the influence of tuberculosis. A study of some of the literature as well as the bioscopic examination in my own case supports the conclusions of others, viz., that although tuberculosis may be a cause of Mikulicz's disease, it is rarely so, and that even a histologic appearance in the glands which strongly suggests tuberculosis is not a positive proof that the disease is present.

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# REVIEWS.

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**MEDICINE: ITS CONTRIBUTION TO CIVILIZATION.** By EDWARD B. VEDDER, A.M., M.D., D.Sc., F.A.C.S., Lieut-Col., M. C., U.S.A. Pp. 388. Baltimore: Williams & Wilkins Company, 1929. Price, \$5.00.

IN 1800, the average length of life in the United States was thirty-three years. In 1924, the expectation of life at birth had increased to 58.1 years. These few figures well exemplify the achievements of medical science in the treatment and prevention of disease. New discoveries will lead to still greater triumphs, but in the meantime much can be gained by the widespread application of knowledge already at hand, particularly as regards personal hygiene and the correction of defects found in periodic health examinations. To accomplish this, "medicine with its ideals and achievements must be popularized." In this book, Colonel Vedder presents the more important facts of preventive medicine for the layman. Part I discusses the causes of disease with chapters on predisposing causes, infectious diseases, nutrition and nutritional diseases, diseases of the glands of internal secretion and the degenerative diseases. Part II takes up the present accomplishment in disease prevention and the problems of the future, with chapters on the conquest of disease, the cancer problem, and modern preventive medicine. The book is well written and by one eminently qualified. The terminology is for the most part intelligible for the layman, but a glossary might perhaps have been added to advantage. Thus the term "filterable virus" is used a number of times previously but is not defined until page 75. As an example of medical progress in the short time since the book was written the Reviewer noted the statement concerning ephedrin: "something of a medical curiosity and not readily obtainable:" today one of the commoner drugs and beginning to be produced synthetically.

R. K.

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**PHYSICIAN AND PATIENT: PERSONAL CARE.** Edited by L. EUGENE EMERSON. Pp. 244. Cambridge: Harvard University Press, 1929. Price, \$2.50.

YEARS ago, the young medical student through his preceptor early became aware of the human relations between doctor and patient and how large a part they play in the art of medicine.



Nowadays, when the Science of Medicine has so filled the student's hours, he is not sufficiently reminded that the practice of medicine has to do with persons as well as diseases. In recognition of this gap in medical teaching, a series of lectures has been given during recent years before the students of the Harvard Medical School by men eminent in the profession. One of these lectures (The Care of the Patient, by Francis W. Peabody, M.D.) has already appeared in print and has been reviewed in these columns. The present volume includes ten lectures: "Some of the Human Relations of Doctor and Patient" (Dr. David L. Edsall); "The Care of Patients: Its Psychological Aspects" (Dr. C. F. Martin); "The Medical Education of Jones; by Smith" (Dr. W. S. Thayer); "The Significance of Illness" (Dr. Austen Fox Riggs); "Some Psychological Observations by the Surgeon" (Dr. Lawrence K. Lunt); "The Care of the Aged," "The Care of the Dying," "Attention to Personality in Sex Hygiene" (Dr. Alfred Worcester). Every senior medical student should be required to read such a book, and should reread it in his intern year. But it could be read with profit by all physicians, by nurses and as the editor suggests, by "all who ever have been sick or ever have anything to do with the sick—pretty nearly everybody, in fact."

R. K.

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DIAGNOSIS AND TREATMENT OF DEFORMITIES IN INFANCY AND EARLY CHILDHOOD. By M. F. FORRESTER-BROWN, Surgeon, Bath, Somerset and Wilts Central Children's Orthopaedic Hospital. Pp. 193; 79 illustrations, Oxford, England: Humphrey Milford, Oxford University Press, 1929. Price, \$4.15.

THIS book is an exposition of principles of orthopedic surgery dealing with diagnosis and treatment, especially preventive. Operative treatment is purposely but briefly described. The book is particularly intended for the general practitioner, the physician interested in infant and child welfare work and the school doctor. The author aptly points out the fact that they have the earliest and best opportunities to see such cases. To these, this book will be a valuable aid. The book is written in a clear and concise fashion and is well illustrated.

J. M.

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THE HISTORY OF HEMOSTASIS. By SAMUEL CLARK HARVEY, M.D., Professor of Surgery, Yale University, New Haven, Conn. Pp. 128; 19 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$1.50.

"Reprinted, with additions" from the ANNALS OF MEDICAL HISTORY, this constitutes an interesting addition to Hoeber's

biographical and topical series that has already frequently been alluded to in these columns. Starting from the Ebers papyrus, the author follows man's efforts to control hemorrhage through the classic periods and that of Western Europe to Paris, Morel and Lister, with especial attention to the tourniquet, hemostat and ligature. Without adding to the sum of our knowledge of hemostasis, the book affords an hour or more of pleasant reading on an important surgical problem. E. K.

THE CYTOARCHITECTONICS OF THE HUMAN CEREBRAL CORTEX. BY CONSTANTIN VON ECONOMO. Professor of Neurology and Psychiatry, University of Vienna. Translated by Dr. S. Parker. Pp. 186; 61 illustrations, 46 of which are photographs. New York: Oxford University Press, American Branch, 1929. Price, \$6.25.

NEW limits are given for the occipital, temporal and parietal lobes, and partly for the olfactory lobe. The cortex is composed of various laminae, "each of which has probably a certain function in the physiological activity of the gray matter." A further subdivision gives different "areas" of which there are more than one hundred. The question in pathology is whether a certain disease causes laminar or areal changes. Amyotrophic lateral sclerosis shows an areal spread while paresis and senile dementia are selective. In the two latter, in Pick's disease, also in dementia precox and chronic alcoholism, it is the third lamina that is particularly involved.

N. Y.

DIAGNOSTIC METHODS AND INTERPRETATIONS IN INTERNAL MEDICINE. BY SAMUEL A. LOEWENBERG, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Jefferson Medical College. Pp. 1032; 547 illustrations. Philadelphia: F. A. Davis Company, 1929.

ANOTHER has been added to the long list of books dealing with diagnostic methods. This volume deals with the physical examination of the various systems, and contains chapters on the interpretation of laboratory findings, radiography, and special industrial and insurance examinations. Only too often the wide scope, which such a work necessitates, proves to be a pitfall for the author, and the immense amount of ground which must be covered results almost inevitably in superficiality. This has been the case in this instance, with the exception of the sections on the respiratory and cardiovascular systems, which have been thoroughly discussed. There are some careless statements and many obscure ones. It will not stand as an authoritative work. E. R.

TEXTBOOK OF CLINICAL NEUROLOGY. By M. NEUSTAEDTER, M.D., PH.D. Clinical Professor in Neurology, New York Polyclinic Medical School and Hospital. Formerly Lecturer in Neurology, University and Bellevue Hospital and Medical College. Pp. 602; 228 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$6.00.

SINCE this volume is written expressly for the medical student and the general practitioner, the conventional textbook arrangement is abandoned so that the symptomatology of each disease is given first.

The subject matter is practical and is clearly and concisely written. An illustration of this may be seen even where description is difficult, as in the comparatively recent and but seldom recognized disease of Schilder—encephalitis periaxialis diffusa.

In the chapters on poliomyelitis, encephalitis and tremors, a distinctly original tone is shown. With his own tremograph the author has made many tracings which are generously distributed throughout the text "and it appears that they always show definite characteristics, irrespective of their fineness or coarseness."

A feature of the book is that it is profusely illustrated, many of the figures are original and all are well chosen. The stated purpose of the volume is admirably fulfilled.

N. Y.

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THE PRINCIPLES OF CLINICAL PATHOLOGY IN PRACTICE. By GEOFFREY BOURNE, M.D., M.R.C.P., and KENNETH STONE, M.D., M.R.C.P. Pp. 392; 10 illustrations. New York: Oxford University Press, American Branch, 1929.

THIS book represents a successful effort on the part of the authors to set down in compact form the clinical pathologic findings usually obtained in the study of disease. A short discussion concerning the pathologic origin is given at the beginning of the section for each disease. Then follows a list of the usual laboratory tests which may be useful in the diagnosis or as a guide in the treatment. Each test is described from the point of view of interpreting the results and of applying them in the diagnosis and treatment of the disease in question. When the procedure is simple and does not require elaborate apparatus, the technique is often briefly stated.

In some diseases suggestions as to treatment are given, usually measures which are suggested by the laboratory findings, that is, the administration of sera, vaccines, and so forth. Related prophylactic measures are also mentioned. At the end of most chapters a short bibliography is given.

The book is written for the practitioner of medicine and records only the "accepted" tests, the choice of which is not always an easy

matter. Thus, in outlining tests of liver function, are given Fouchet's test, the van den Bergh test, levulose and galactose tolerance tests, and the glycuronic acid reaction. No mention is made of the tetrachlorophthalein test, Widal's "crise hemoclasique" or icterus index test. The significance of urobilin in the urine is said to be doubtful.

The volume is easily readable, and presents its subject in such a useful and practical way that it should prove a valuable aid to both practitioner and student.

L. F.

THE MODERN DANCE OF DEATH. By PEYTON ROUS. Pp. 51.  
Cambridge: The University Press, 1929.

To those who, often with justice to be sure, cavil at the style in which American medical scientists present their material, the author can be pointed out as a shining exception. And nowhere does this pleasant capability stand out better than in the Linacre lecture that this booklet presents. A sympathetic yet critical appreciation of the various Dances of Death so prevalent in Linacre's time precedes a thoughtful and artistically expressed consideration of various new and often unexpected aspects of pathologic physiology. These, brought about by man's rather sudden acquisition of operative and biologic control over his normal and morbid processes, show that Death's dancing partner is no longer passive as in the ancient prints. The physician's increasingly apparent duty, that of keeping old bodies fit, will thus produce a new Dance of Death, though the author is one with his old master, Warthin, in viewing much of the aging process as inevitable.

E. K.

AN INDEX OF SYMPTOMATOLOGY. By VARIOUS WRITERS. Edited by H. LETHEBY TIDY, M.A., M.D. (OXON.), F.R.C.P. (LOND.), Assistant Physician, St. Thomas' Hospital; Consulting Physician, Royal Northern Hospital. Pp. 710; 130 illustrations; 4 colored plates. New York: William Wood & Co., 1929. Price, \$12.00.

It is attempted in this work to give a definition and a brief description of the clinical picture of diseases, adequate for enabling the practitioner to recognize a fairly typical case. Written by twenty-six contributors, engaged in the practice of the various specialties, the work covers all the branches of medicine, surgery, gynecology and the special subjects. The material is presented by diseases or diagnoses, arranged alphabetically from "Abdominal Injuries" to "Yellow Fever." The descriptions are for the most

part well done. The illustrations are excellent. That omissions should occur in the first edition of a book covering so wide a field is not to be wondered at: it is indeed surprising that there are so few. Some that the Reviewer noted are: cervical rib, foreign bodies in the bronchial tree, inguinal granuloma, the relation at times existing between lung abscess and lung neoplasm, the work of Goldberger on the etiology of pellagra. The book should be valuable for quick and handy reference in diagnostic problems. R. K.

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LABORATORY MANUAL OF THE DIVISION OF BACTERIOLOGY, PEKING UNION MEDICAL COLLEGE. Prepared under the direction of C. E. LIM, Peking Union Medical College. Pp. 154; 20 charts. Peking, China: Peking Union Medical College Press, 1929. Price, \$1.50.

THIS book is a manual of the bacteriologic and serologic methods in use at the Peking Union Medical College Hospital. It is printed on a good grade of paper in easily read type, and is bound serviceably. There are a few inconsequential typographical and linguistic errors.

The contents include directions for all the common bacteriologic and serologic procedures, in most instances only one technique being given—their preferred method. This naturally is not in all instances the preferred method in all laboratories. The subject of protozoölogy is not included.

The directions are concise and easily followed.

It would have been well to include more detailed directions in some cases, as in the clearing of culture media, for instance.

The classification of bacteria is for the most part not carried very far, rather rough clinical classifications being followed—streptococci merely as hemolytic and nonhemolytic, for example.

There is a useful chapter upon the care of animals and cost of upkeep, such as is seldom found in the smaller books on laboratory methods.

F. L. JR.

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ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY. Volume IV, Part II. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London; and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 241; 18 plates (full page). Baltimore, U. S. A.: The Williams & Wilkins Company, 1929.

VOLUME IV of these *Annals*, devoted to the pathogenic streptococci, is presented in two parts. The streptococci have been ex-

amined in relation to the different diseases with which they can be identified, and a separate monograph compiled on each disease. Part I (previously reviewed, see April, 1929, p. 576) contains four monographs. Part II, which consists of three monographs, deals with the rôle of the streptococci in acute suppurative arthritis and in chronic rheumatism, including rheumatoid arthritis and osteoarthritis. Rosenow's hypothesis of elective localization is also reviewed.

These monographs give a complete résumé of the researches which have been carried out since the beginnings of bacteriology, and are not confined to the streptococcal theories alone, but supply an account of most of the important views and theories held by various clinicians. The volume, therefore, comprises much information which should not only be of interest to the bacteriologist but to the clinician as well; it also contains a very large bibliography of over 1600 references, an author's index, and a very complete subject index.

Special attention is drawn to the original work of Warren Crowe on osteoarthritis and the author's simple new differential test for the streptococci. With Vol. III, Vol. IV, Part I (completed), and Vol. V, VI and VII (to be published), Vol IV, Part II is important as a unit in the proposed comprehensive study of pathogenic streptococci which will undoubtedly aid materially in identifying the great majority of the many varieties of streptococci. W. K.

## BOOKS RECEIVED.

### NEW BOOKS.

*Interns Handbook.\** Under direction of M. S. DOOLEY, A.B., M.D. Pp. 235. Philadelphia: J. B. Lippincott Company, 1929. Price, \$3.00.

*Surgical Diseases of the Thyroid Gland.\** By E. M. EBERTS, M.D. Pp. 238; 48 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$3.50.

*The Female Sex Hormone.\** By ROBERT T. FRANK, A.M., M.D., F.A.C.S. Pp. 338; 86 illustrations. Springfield, Ill: Charles C. Thomas, 1929. Price, \$5.50.

*La Terapia Epatica e le sue Applicazioni con Particolare Riguardo all' Anemia Perniciosa Series 1 N. 27.\** By PAOLO INTROZZI. Pp. 74.

*Medical Clinics of North America (Chicago Number) Vol. XIII, No. 2, September, 1929.* Pp. 232; 61 illustrations. Philadelphia: W. B. Saunders Company, 1929.

*What Everyone Ought to Know.\** By OLIVER T. OSBORNE, M.D. Pp. 313. Springfield, Ill: Charles C. Thomas, 1929. Price, \$2.50.

\* Reviews of titles followed by an asterisk will appear in a later number.

*Oxford Monographs on Diagnosis and Treatment.* Vol. V. Edited by HENRY A. CHRISTIAN, M.D., Sc.D. LL.D. *The Diagnosis and Treatment of Chronic Diseases of the Respiratory Tract.\** By ELMER H. FUNK, M.D. Pp. 618; 182 illustrations. New York: Oxford University Press, American Branch, 1929.

*The Layman Looks at Doctors.\** By S. W. and J. T. PIERCE. Pp. 251. New York: Harcourt, Brace & Co., 1929. Price, \$2.00.

*Première Conférence Internationale de la Lumière. Physique, Biologie, Thérapeutique, Lousanne et Leysin, September 10-13, 1928.* Pp. 543. Illustrated. Française, Paris: L'Expansion Scientifique, 1929. Price, 10 francs.

In the 8 seances and conferences are included some two score reports and communications by specialists of many nations, a number of whom are internationally known.

*Progressive Medicine, Vol. III. September, 1929.* Edited by HOBART AMORY HARE, M.D., LL.D. Pp. 327. Illustrated. Philadelphia: Lea & Febiger, 1929.

*Tularemia.\** By WALTER M. SIMPSON, M.S., M.D., F.A.C.P. Pp. 162; 55 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$5.00.

*The Doctor in Court.\** By EDWARD HUNTINGTON WILLIAMS, M.D. Pp. 289. Baltimore: Williams & Wilkins Company, 1929.

## NEW EDITIONS.

*Text-book of Embryology.* By F. R. BAILEY, A.M., M.D., and A. M. MILLER, A.M. Pp. 687; 529 illustrations. Fifth edition. New York: William Wood & Co., 1929. Price, \$7.00.

*Diseases of the Stomach.* By MAX EINHORN, M.D. Pp. 593; 131 illustrations. Seventh edition. New York: William Wood & Co., 1929. Price, \$6.00.

*Practical Local Anesthesia and Its Surgical Technic.* By ROBERT EMMETT FARR, M.D., F.A.C.S. Pp. 611; 284 illustrations. Second edition. Philadelphia: Lea & Febiger, 1929. Price, \$9.00.

*The Nutrition of Healthy and Sick Infants and Children.\** By E. NOBEL, C. PIRQUET and P. WAGNER. Translated by BENJAMIN M. GASUL, B.S., M.D. Pp. 243; 78 illustrations. Second revised edition. Philadelphia: F. A. Davis Company, 1929. Price, \$3.50.

*Clinical Medicine for Nurses.* By PAUL H. RINGER, M.D. Pp. 330; 16 illustrations. Third edition. Philadelphia: F. A. Davis Company, 1929. Price, \$3.00.

*Memoranda of Toxicology.* By MAX TRUMPER, B.S., A.M., Ph.D. Pp. 214. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1929.

*The Chemical Aspects of Immunity.\** By H. GIDEON WELLS, Ph.D., M.D. Pp. 286; second edition. Chicago: Chemical Catalogue Company, 1929. Price, \$6.00.

\* Reviews of titles followed by an asterisk will appear in a later number.

# PROGRESS

OF

## MEDICAL SCIENCE

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### MEDICINE

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UNDER THE CHARGE OF

W. S. THAYER, M.D.,

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AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

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**The Wassermann Reaction of Human Milk.**—A comparison of blood and milk tests in 107 cases. It is obvious that examination of the milk of a puerperal patient affords a convenient method of determining the presence of syphilis. The only question that might arise would be whether or not the reaction with milk would be as exact as with blood serum. The first thought would be that the amount of fat in milk might in some way affect the reaction. That this is not the case is proven by a recent paper by JARCHO (*J. Lab. and Clin. Med.*, 1929, 14, 1097), who shows that there is rather a close parallelism between the Wassermann reaction on the milk of puerperal women and the blood. One hundred and seven examinations were made and 95 per cent of the cases agreed in substance and there was exact qualitative-quantitative agreement in 89 per cent. Three times the milk was positive and the blood negative, while only twice was the blood positive and the milk negative. In addition to the convenience of obtaining material for examination, it is also true that the test should be practical for the testing of the milk of prospective wet nurses.

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**The Effect of Exercise on the Size of Normal Hearts and of Enlarged Hearts of Dogs.**—For many years clinicians have been interested in the possibility of exercise producing changes in the heart. Long-continued exercise or training carried to excess will always produce a change in heart weight-body weight ratio. However, this statement does not apply to animals or men who have recently undergone a relatively short but severe form of exercise. STEWART (*J. Clin. Invest.*, 1929, 7, 339), using somewhat different methods than have been employed in the past, has reopened the question and investigated the effect of exercise not only on the normal heart but on the heart of dogs in which lesions



of the mitral valve have been produced through operation. The experimental animals were taught to run on a treadmill. The hearts were Roentgen rayed according to a method described by the author two years ago. These Roentgen ray photographs were made before the dog began running on the treadmill, immediately afterward and after rest of an hour. The animals ran steadily from twenty to sixty minutes. In normal dogs there was a quite marked diminution in the size of the heart after the voluntary exercise. For example, in one dog immediately afterward there was a fall to 94.8 per cent of the initial size followed by a further decrease to 92.8 per cent. In dogs with already increased hearts in which systolic murmurs were present, figures comparable to those in the normal dog were obtained. The same statement holds true with the effect of exercise on the size of the heart in dogs who have been subjected to operation, but in which the valvular difficulty cannot be demonstrated. If, then, there was diminution in the size of both normal and enlarged hearts in which there was presumably no myocardial disease and no signs of heart failure, it is fair to assume that dilatation of the heart occurs only in that organ in which disease has produced changes in the myocardium.

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## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,  
PHILADELPHIA, PA.

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**A Clinical Consideration of Urinary Antiseptics.**—KAUFMAN (*J. Urol.*, 1929, 22, 163) says that the general practitioner as a rule first sees the common forms of infection of the urinary tract. It is essential that he be familiar with the limits of general treatment. Treatment of urinary infection demands primarily recognition of the factor of drainage. Water is essential with certain physiologic aids in combating pyrexia, toxemia and renal failure. Urinary antiseptics serve an important purpose in the treatment of both acute and chronic infections. They are now clearly established on both scientific and clinical grounds.

**On Dilatation of the Ureters and Hydronephrosis in Childhood.**—MACMYN (*Brit. J. Urol.*, 1929, 2, 150) claims that the condition is not common but may frequently be overlooked; and being unsuspected may rapidly reach a fatal termination. Its recognition is only possible after careful urologic investigation, which includes all the modern methods of examination at our disposal. The condition is marked by disorders of micturition, due to obstruction and superadded infection. A valvular obstruction in the posterior urethra is regarded as being more common than has been previously supposed and is held to account for many cases of dilatation of the urinary tract hitherto ascribed to other causes.

In postmortem examinations of cases where the obstruction is not at first apparent, a careful dissection of the urethra is essential. The whole urinary tract should be removed *en masse* for this purpose. The disease is especially liable to be associated with other congenital abnormalities, whether in the urinary tract or elsewhere in the same child. Modern methods of diagnosis favor a more early recognition of the disease and afford the urologist a better chance of success in its treatment.

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**Osteitis Fibrosa and Giant-cell Tumor.**—GESCHICKTER and COPELAND (*Arch. Surg.*, 1929, 19, 169) find that in an analysis of over 400 cases of tumor in the giant-cell group, a pathologic relationship was established between the bone cyst, giant-cell tumor of the long bones and skull, giant-cell epulis of the alveolar borders and giant-cell tumors of the tendon sheaths. The usual bone cyst occurring in the metaphyseal region of the long bones of young patients, was shown to be a healing phase of giant-cell tumor—a conclusion based on clinical, pathologic and anatomic observations and demonstrated by an analysis of numerous transitional lesions between these two entities. Giant-cell tumors of the skull and long bones, epulides of the alveolar border and giant-cell xanthomas of the tendon sheaths were found to be fundamentally related to a transitional process characterizing the histogenesis of bone via the indirect route of substitution bone. This transition process underlying all these tumors, as shown by embryologic studies, involves a proliferation of giant-cell osteoclasts, the function of which is to initiate the canalization and vascularization of the preliminary calcified structure.

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**A Treatment of Persistent Bronchial Fistula.**—POOL and GARBOCK (*Ann. Surg.*, 1929, 90, 213) state that bronchial fistulas occur most commonly with empyema thoracis and lung abscess. The majority close spontaneously. Persistence of a fistula may be due to suppuration in the parenchyma of the lung or the bronchial tree, the presence of a rigid-walled empyema cavity with which the fistula opens, the formation of a bronchocutaneous channel or the presence of a foreign body. Operative closure of a bronchial fistula should not be attempted until the need for drainage of a lung suppuration has passed. Very small fistulas will frequently close following the local application of some cauterizing agent. For the closure of a bronchial fistula which persists in spite of conservative measures, an operative procedure is described. This consists in plugging the fistula with a pedunculated muscle flap. The operation is simple, of wide application and has proved successful in the authors' experience. The production of a bronchial fistula in an experimental animal is attended with great technical difficulties. Although the experimental data herewith reported do not duplicate exactly conditions as found in man, the results obtained indicate clearly the processes of repair following closure of a bronchial fistula by the method described. A muscle flap placed in a bronchial fistula to effect its closure remains viable and is not completely replaced by fibrous tissue.

## THERAPEUTICS

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UNDER THE CHARGE OF

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AND

SOMA WEISS, M.D.,

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**The Rectal Administration of Liver and Liver Extract in Pernicious Anemia.**—PULVER (*Therap. d. Gegenw.*, 1929, 70, 294) reports on his favorable experiences with the rectal administration of liver or liver extract. This channel of administration is indicated in patients unable to retain the orally administered liver or liver extract. The impetus for the study of this problem was the observations on two patients (reported before) with severe manifestations of pernicious anemia, who failed to respond with improvement after oral administration of liver, but who showed marked improvement when the liver was administered rectally. This method of administration consists of passing the crushed raw liver mixed with milk and 20 drops of tincture of opium through a sieve and introducing this mixture slowly through a high rectal tube after a preliminary cleaning enema. Instead of raw liver, correspondingly potent liver extract may be used. Liver extract suppositories were also used. It is advisable to leave the rectal tube inserted for some time and to remove it slowly and gradually. If the patient develops diarrhea the rectal administration should stop for a day or two. Most people retain the therapeutic liver enema well. Old people occasionally exhibit rectal pain because of the presence of hemorrhoids and diarrhea. The author reports his experiences on 11 patients. In conclusion he lays emphasis on the fact that the success of the liver therapy often depends on the amount administered. The optimal dose varies according to the individual patient and his condition. In rare instances as high a dose as 1 kg. of raw liver or equivalent liver extract may be required for prompt response.

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**Hemostatic Therapy in Hemophilia.**—PAYNE and STEEN (*Brit. Med. J.*, 1929, i, 1150) investigated the effect of hemoplastin, "coagulin-Ciba," "fibrinogen Merrell" (tissue fibrinogen), horse serum, protein shock, calcium, citrated human blood, and citrated human plasma on the coagulation time of 4 patients with hemophilia. None of the above agents exerted a permanent effect. The only form of treatment that was found to be of any real value was intravenous injection of either citrated whole blood or citrated human plasma. Citrated plasma given intraperitoneally or intramuscularly was without effect. Citrated human plasma has the advantage of not requiring a preliminary blood grouping, and the use of human plasma prevents any danger of anaphylaxis. Both

with whole blood and plasma no stage of hypocoagulability occurs. The authors conclude that the most effective agents, both for treatment and pre-operative prophylaxis, are citrated whole blood and citrated plasma given intravenously.

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**The Toxicity of Different Arsphenamin (Salvarsan) Solutions.**—It is well recognized that the method of the preparation of arsphenamin solutions has an important bearing on the toxic and therapeutic effect of arsenical compounds in animals and in man. DREXFUS (*Münch. Med. Wchnschr.*, 1929, 1, 1285) reports his clinical experiences with different solvents used in arsphenamin therapy.

Although the use of tap water as a solvent is tolerated by most patients without untoward symptoms, it cannot be recommended for general use. The presence of small amounts of potassium and magnesium salts in the tap water may increase the toxicity of arsphenamin. Occasionally, the presence of small solid particles may be the source of minute emboli. Redistilled water should, therefore, be preferred.

Animal experiments indicate that arsphenamin dissolved in sugar solutions is less toxic. For clinical purpose 15 to 40 per cent glucose solution proved very useful. The use of arsphenamin dissolved in 20 to 25 c.cm. of a 40 per cent glucose solution is especially indicated in: (1) patients who are hypersensitive to arsphenamin; (2) patients with cardiovascular diseases; (3) patients who after malaria inoculation have to receive large doses of neoarsphenamin as complimentary treatment. Instead of glucose, lactose may be used. Both glucose and lactose solutions are less toxic than watery solutions, although the therapeutic value of the arsphenamin is unchanged.

The use of a 10 per cent calcium chlorid solution as a solvent for neoarsphenamin is advocated in patients who are hypersensitive to this drug.

The author claims that the use of certain iodine solutions as solvents increase the therapeutic efficiency of arsphenamin.

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## PEDIATRICS

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UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

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**General Edema in Association with Tetany of the Newborn.**—SHANNON (*Arch. Ped.*, 1929, 46, 549) says that the term "Edema Neonatorum" has come into the minds of many to signify a rare disease entity occurring almost altogether in premature or immature infants and bearing in its fullest development little resemblance to ordinary edema. It has such a high mortality that when seen the prognosis is most unfavorable. In many textbooks this is the only reference made to edematous conditions occurring in the neonatal period. As a result,

an entirely wrong opinion is apt to be acquired concerning the edemas as they occur in the newborn. Some writers appreciating this fact have separated this condition entirely from the edemas of the newborn and consequently have given a much more accurate conception of the latter. Among these authors are von Reuss and Feer who recognize edema as one of the common affections of the newborn period without particularly serious significance. They attribute its occurrence to a deficiency in the salt-excretion function at this age. Since edema is a common condition in the neonatal period, not necessarily confined to premature and immature infants, the author feels that it is a grave error to use such a valuable a term as "Edema Neonatorum" for a rare disease complex which is so singularly unlike edema as it usually occurs. In this paper he reports three cases of generalized edema in newborn infants. In each of these the edema accompanied most generally symptoms of tetany and in each it disappeared promptly along with the tetanic manifestations under calcium and parathyroid therapy. This result was obtained in spite of the fact that two cases presented other possible causes of the edema which have been frequently mentioned as being responsible for edema in the newborn. One case had a congenital heart, while the other had definite evidence of kidney pathology. As a result Shannon feels that calcium deficiency may be one of the causes of generalized edema occurring during the newborn period. He also claims that tetany is common enough during this period for this cause to be frequently met. He also suggests the possibility that cerebral edema may be responsible for certain cyanotic attacks seen during the neonatal period.

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**A Soy Bean Preparation for Feeding Infants with Milk Idiosyncrasy.**  
—HILL and STUART. (*J. Am. Med. Assn.*; 1929, 93, 985) remind us that soy bean flour was originally used in this country by Ruhräh in the form of a gruel in the treatment of diarrhea in 1910. Previous to that time it had been used in one form or another in China as a supplementary infant food for many years. In a case of milk idiosyncrasy under the care of Dr. Hill an attempt was made to prepare a dried infant food that would be complete in meeting the child's requirements and yet be free from animal protein. Soy bean flour was chosen as a most promising food from which to obtain the protein necessary. With the assistance of Dr. James L. Gamble a formula was devised that was satisfactory for the theoretical requirements of infants. Sufficient soy bean flour was used to give a protein percentage of 4 in the finished product and diluted food. This percentage, higher than that normally present in milk, was adopted because of the differences in the amino-acid content of the two proteins and in order to assure ample amounts of each of the necessary ingredients the salt content of cows' milk and soy bean flour was studied in order to determine the additional salts required. It was found that magnesium, potassium and phosphorus are present in sufficient amounts but that there is a deficiency in calcium, sodium and chlorin. In order to overcome this the addition of calcium carbonate, 2 gm., and sodium chlorid, 1 gm., was made for each 100 gm. of solids. The vitamin content of soy bean flour if properly prepared and cooked has been shown to be adequate by the studies of Osborne and Mandel. In order, however, to compensate for possible differences in the content

of the fat-soluble vitamins in different samples, which varies with the completeness or incompleteness of the removal of the oils in the preparation it was suggested that cod-liver oil be given regularly but it was not included in the composition of the food but is recommended to be used as an additional food substance along with orange juice. In order to meet the additional energy requirements the fat content of the food was raised by the addition of olive oil in quantities sufficient to make the final fat content in the diluted food 3 per cent and barley flour in quantities sufficient to make the final carbohydrate percentage about 4 per cent. Sugar was purposely omitted because it was felt that it would be better to leave the determination of the amount and kind of sugar to be added to the discretion of the physician so as to meet the needs of individual infants with varying degrees of tolerance for carbohydrate. The authors feel that sugar in some form should always be added unless the infant has sugar intolerance. This preparation has been used for a year to the entire satisfaction of the writers, who have observed that stools are likely to be somewhat more frequent than seen in babies on cows' milk but rarely amounting to diarrhea. In babies under eight months of age they have not started with the full strength formula but recommend two-thirds strength and in small babies it is advised to start at half strength. This concentration may soon be increased. In all, they report 40 babies fed on this food and remark that they have done well. They feel that they are not justified in stating that this milk is as good a food for infants in general as the ordinary formulas made from cow's milk but they do feel that it is a very efficient and practical substitute when it is impossible to use milk. This was especially noted in babies with eczema.

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**Epilepsy in Children.**—MCQUARRIE and HUSTED (*Am. J. Dis. Child.*, 1929, 38, 451) studied the superficial relationship between water balance and the occurrence of seizures in a number of epileptic children. There seems to be a tendency for the epileptic patient to retain water during the active phase of the disease in amounts which are harmful. Convulsions tend to occur when a positive water balance above a certain amount is established. When diuresis follows the attack further seizures are prevented temporarily. They could not state that the effect of the extra water is due solely to changes within the brain. Procedure such as fasting, the use of ketogenic diets and the stringent restriction of water with nonketogenic borderline diets led to partial dehydration of the tissues and prevention of seizures. They observe that the sudden increase of the water intake during treatment by dehydration caused recurrence of seizures at least in the severe cases. Parenteral administration of pituitary or of the antidiuretic hormone of the hypophysis caused the development of a positive water balance and the occurrence of seizures. Urea in large doses caused the loss of retained water. They feel that there is a definite relationship of water balance and the etiology of epilepsy.

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**The Relationship of Jaundice and Weight to Blood Values in the Newborn Infants.**—MITCHELL (*Am. J. Dis. Child.*, 1929, 38, 518) made red cell counts and hemoglobin estimations of the blood of 69 infants on the first, third, seventh and tenth day of life. He also studied the

volume percentage of the cells in the blood in 50 newborn babies. He found that the cell volume was considerably greater than the average for adults and the volume index was also high. He found that infants with jaundice did not show lower average red cell and hemoglobin values than those without jaundice. Practically all babies showed a loss of red cells and hemoglobin between birth and the tenth day of life but the average loss of those with marked jaundice was only slightly greater than of those without jaundice. Changes in weight were accompanied by changes of red cells in infants showing the same degree of jaundice. Babies with marked jaundice showed a much smaller gain over their weight at birth than babies on the tenth day than babies without jaundice. Dehydration when of a degree to show clinical manifestations with fever showed a marked influence on the red cell count.

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## DERMATOLOGY AND SYPHILIS

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UNDER THE CHARGE OF

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**Drug Reactions from Barbitol (Veronal) and Phenobarbital (Luminal).**—POOLE (*Yale J. Biol. and Med.*, 1929, 1, 345) states that within the last sixteen years, the barbitol drugs have achieved a wide popularity and while the doses in recent years have been less than the former large doses, reactions still occur in upwards of 3 per cent of the cases (Menninger). There are two types of reaction, a general systemic reaction with signs of acute poisoning, and skin reactions with or without mild systemic disturbances. Most of the severe reactions have occurred after large doses, yet frequent reactions are reported in patients receiving but  $1\frac{1}{2}$  grains a day. Reactions occur within twenty-four hours, or as late as eighty-one days. The author reports 11 cases, 4 showing the skin type of reaction (all luminal cases) and 7 cases of general reactions (3 luminal and 4 veronal). The cases with severe general reactions had no dermatitis, while the dermatitis group showed a slight or moderate general reaction, such as fever, nausea, vomiting, diarrhea, headache, stomatitis and conjunctivitis. Leukocytosis and eosinophilia were often present. One of the skin reaction cases with an exfoliative type of dermatitis came to autopsy. The exfoliative reaction was found to involve the bronchi, kidney pelves and ureters, and the observer suggests that the mechanism of death in exfoliative dermatitis is bronchial obstruction and not bronchopneumonia. One of the reported cases was the occurrence of a skin reaction with moderate systemic symptoms

in a girl, aged fifteen years, who was taking both luminal and Fowler's solution. To determine the rôle of luminal in this instance an intradermal skin test was made. This was done using a 2 per cent aqueous solution of sodium luminal (hypodermic tablet). Approximately 0.02 cc. was injected intradermally on the flexor surface of the forearm with a control of physiologic saline on the other arm. Two minutes after the injection an urticarial wheal with pseudopod formation developed at the point of injection of the luminal solution. The wheal increased rapidly in size, remained unchanged in size for two hours and then gradually disappeared. The author concludes that the mechanism of the reaction in the poisoning cases is relatively clear but in the dermatitis cases, the relative infrequency, the type of skin rash, the blood picture and the reaction to intradermal skin tests suggests a drug idiosyncrasy, allergic in nature.

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**Concerning the Cultivation of *Spirocheta Pallida*.**—KAST and KOLMER (*Am. J. Syphilis*, 1929, 13, 419) report their failure to cultivate *Spirocheta pallida* from human and rabbit lesions, despite numerous and persistent attempts for a period of five years. In all, sixteen different culture media were employed, all the media were incubated for from one to three days before inoculation, all were kept at 37° C. and all but two were sealed with vaselin after inoculation. In their work no true multiplication of spirochetes occurred in any medium. Saprophytic spirochetes, simulating *Spirocheta pallida*, could be cultivated. In reviewing the literature from 1906 to date, the authors feel that with the exception of Noguchi's work possibly many of the reported cases of alleged *Spirocheta pallida* cultivation were in reality cultures of a finer saprophytic type. A comprehensive and detailed abstract of the work of thirty-three investigations from the literature is included.

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**Febrile Body Temperatures as Possible Adjunct Treatment in Wassermann-fast Syphilitic Patients.**—CADY and EWERHARDT (*Am. J. Syph.*, 1929, 13, 313) conducted a series of hot baths on 13 patients with syphilis. With one exception all the cases were of the chronic type and designated Wassermann-fast. The bath temperatures varied from 104° to 107° F. at the outset with subsequent bath temperatures of 104° to 111° F. The body temperature rose to 102.3° to 106° F. in twenty to forty minutes. In general the bath was continued at the highest tolerated temperature for twenty to forty minutes. The pulse rate rose in proportion to the body temperatures. No serious adverse reactions were encountered. The authors present their data in the form of thirteen complete histories and protocols with no general tabulation of results. Their investigations did not reveal any consistent evidence that hot baths were useful in Wassermann-fast patients. They believe that the serologic reactions were rendered more labile during relatively short periods of thermotherapy. The fact that there was an improvement in the patient's sense of well-being and an apparent serologic response in a small percentage of their cases has encouraged the investigators to continue their investigations on this mode of therapy.



## GYNECOLOGY AND OBSTETRICS

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**Radiation Treatment of Fibromyomata.**—Although the radiation treatment of uterine fibromyomata is now firmly established in the properly selected cases, a large series of such cases is always worthy of at least passing notice. In a series of 604 cases which have been treated by SOILAND, COSTLOW and MELAND (*California and West. Med.*, 1929, 30, 234) by means of radiant energy including low voltage Roentgen ray, high-voltage Roentgen ray, radium alone and radium with Roentgen ray, they were able to trace 562 patients and have tabulated their results, which were quite satisfactory. In 5 cases in younger women with small fibroids who gave dysmenorrhea as their only symptom and had a return of their menstruation after the treatment, four were found to be entirely relieved of the dysmenorrhea. In only 1 case in the series was pregnancy associated with the fibroid tumor and she miscarried, but she had a positive Wassermann and had miscarried three times previously. They believe that it takes some time for the complete disappearance of the tumor mass, probably about five years. Bleeding continued in 10 cases, necessitating a hysterectomy; 6 of these proved to be malignant (carcinoma of the fundus). In the entire series of 562 cases only 13 (2.3 per cent) failed to respond to the treatment. It is their experience that the combination of radium and deep Roentgen ray therapy is the best type of radiation treatment in the majority of cases. While radiation is the treatment of choice in tumors not larger than a four-month pregnancy, they state that the majority of tumors larger than this size may be rendered symptomless by this treatment. This is worth remembering in the presence of a large bleeding tumor in a patient who is not a fit subject for surgery.

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**Intraäbdominal Insertion of Radium in Cervical Cancer.**—In an attempt to eradicate deeply situated carcinomatous infiltration resulting from cervical cancer, DONALDSON (*Brit. Med. J.*, 1929, i, 844) has developed a technique for the intraäbdominal application of radium. This is usually carried out about six to eight weeks after the vaginal application, that is to say, when the local growth has disappeared and all the ulceration has healed. No attempt has been made so far to combine the intraäbdominal application at the same time with the vaginal treatment merely on the theoretical grounds that while there is an infected area in the cervix and fornices it is not wise to do anything to the abdomen and parametrium which might lower the resistance to that infection. The patient is put into the Trendelenburg position and

the abdomen is opened. A general examination is made of the liver and aortic glands in addition to the pelvic organs and the iliac glands. The intestines are packed off and the uterus is pulled forward; the parietal peritoneum is then picked up with forceps and the radium needle inserted, leaving only the eye of the needle protruding from the peritoneum. A suture is placed through a small portion of peritoneum below the level of the needle eye and the knot is tied over a glass bead to prevent cutting through the thin peritoneal tissue. Other radium needles are placed at a distance of from 1 to  $1\frac{1}{2}$  cm. from each other, starting at one sacroiliac synchondrosis and ending at the corresponding joint of the opposite side. In addition, four or more needles are placed in front of the broad ligaments in the hope of eradicating the disease from the obturator glands. The ends of the ligatures are tied together and pushed down into the pouch of Douglas. The abdomen is completely closed and the radium left *in situ* for seven days. At the end of this time the abdomen is again opened and the radium is removed. An objection to this technique is the second laparotomy at the end of a week, but up to the present it has been felt that in order to keep them in position the needles should be sutured to the peritoneum which makes it impossible to pull them out. In addition to this they are often placed at an angle to the line of traction and damage might be done if they were pulled out blindly.

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## RADIOLOGY

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**Light Deficiency as the Principal Cause of Osteomalacia in India.**—Osteomalacia is known throughout India, and is especially severe in Kashmir, where almost all the better class of women are more or less affected. In her paper VAUGHAN (*Brit. J. Actinotherapy and Physiotherapy*, 1929, 3, 243) shows that this condition is due to want of light. The disease begins at puberty or before and roughly coincides with marriage. It commences with vague pains in the bones and backache, and is often mistaken for rheumatism. The girl is always anemic and frequently complains of spasm of the hands. Digestion is bad. Gross changes are exhibited in the bones of the limbs which become bent and twisted. In the pelvis, which becomes soft like wax, the bones are pressed together laterally by the heads of the femora until the pubic rami are almost in apposition, the space between the ischial tuberosities is greatly reduced, the lower lumbar vertebræ are displaced forward, and childbirth becomes impossible. The women in India who suffer from osteomalacia are those whose social customs make it imperative

for them to live indoors. She can never go out and sees but few people. If her husband is poor she remains behind a curtain in the back of his one room, completely deprived of light and air, or she may have a dark room with no window. The pains of osteomalacia are worse in the winter and improve in the summer, in the Kashmir valley. In the winter the women of this class cover their lattice windows with oiled paper or hang felt rugs over them. There is little sunlight and the valley is shrouded in mist and fog. It is important to note, on the other hand, that among the poorer classes of Kashmir who work in the open air such a condition as osteomalacia is unknown; the women are healthy and easily bear from 8 to 20 children.

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**Rugæ Gastricæ: Their Importance in Roentgenologic Diagnosis.**—The study of the gastric rugæ, according to GOLOB (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 33) is a much neglected field, yet it may assist materially in gastroenterologic diagnosis. For their demonstration it is necessary that the amount of barium in the region examined be relatively small. The examiner may use either a small quantity of the contrast meal, or a thin suspension of barium, or thin out the usual dense mixture by manual pressure over the median and prepyloric segments of the stomach. Lenk and Eisler have shown that the rugæ in the immediate vicinity of an ulcer are not parallel, as normally, but converge toward the ulcer. Distortion or localized effacement of the rugæ usually bespeaks induration or infiltration of the mucosa. This sign is especially important when it is associated with a localized absence of peristalsis. In the cardiac region of the stomach, distortion of the rugæ, coupled with deformity of the gas bubble, practically clinches the diagnosis of an organic lesion.

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**Roentgen Diagnosis of Intrathoracic Neoplasms.**—Pulmonary cysts of congenital origin, teratomata, dermoids and unruptured hydatid cysts present quite characteristic roentgenologic appearances, according to FARRELL (*Radiology*, 1929, 13, 1). Mediastinal tumors of lymphatic origin are also fairly characteristic; they respond well to Roentgen therapy, and an exposure to a therapeutic dose of Roentgen ray may make possible a differential diagnosis between these tumors, substernal thyroid and extrabronchial carcinoma. Metastases of some varieties, notably the nodular and miliary, are readily diagnosed. Infiltrative and massive changes in the lungs, while not always definitive of themselves, are pathognomonic when associated with a known primary malignant tumor of some other organ. Extrabronchial pulmonary carcinomata, while they usually have characteristics which establish them as new growths, may be confounded with mediastinal lymphatic tumors. Endobronchial (bronchial) carcinomata present the greatest problem in the diagnosis of intrathoracic tumors. The signs which they present depend on their age and point of origin. The direct sign of endobronchial carcinoma is a mass due to the presence of a tumor, to which collapse, infection or metastasis may be traced as secondary phenomena. The indirect signs are similar to those of bronchial foreign body.

## NEUROLOGY AND PSYCHIATRY

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**Further Light on the Transmission of Pain and Temperature within the Spinal Cord: Human Cordotomy to Abolish Pain Sense without Destroying Temperature Sense.**—STOOKEY (*J. Nerv. and Ment. Dis.*, 1929, 69, 552) presents 4 cases in which cordotomy was performed for the relief of intractable pain. Two had unilateral and 2 had bilateral cordotomies. The operation is performed in the unilateral cases through a Taylor's hemilaminectomy. A small, straight, knife is used. "A delicate lateral incision just ventral to the dentate ligament is made and the knife brought out just lateral to the ventral horn. By varying the depth of the incision, one may vary the segmental level of the anesthesia, since apparently the more distal segments lie nearest the periphery of the cord." In none of his cases was temperature sense involved after operation. He concludes that the pain sense is carried in the lateral spinal thalamic tract and that temperature sense is carried in a tract more ventrally placed, which may be the ventral spinal thalamic tract. He prefers the use of the small, straight knife in the operation because the sickle-shaped knife recommended by Fraser cuts a considerable amount of cord substance beyond that necessary and does not permit of accurate control of the incision.

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**Industrial Psychiatry.**—ELKIND (*Mental Hygiene*, 1929, 13, 378) calls attention to the contributions psychiatry has made to industry in diminishing the number of compensation neuroses, in the study and treatment of industrial poisoning and in the detection of malingering. In the management of industrial personnel the psychiatrist concerns himself with normal people. Here the main consideration is one of adaptation of an individual to his position, where generally a new adjustment may be necessary. He cites Anderson's work as an example of the fact that it is not only in the field of selecting that psychiatry may be applied, but also in the follow-up supervision of the individuals during their periods of adjustment and readjustment in the industry. He cites a few cases illustrative of readjustment of individuals who had difficulties at work.

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**Ueber Tetanie und Tetaniepsychosen.**—FUNFGELD (*Archiv f. Psychiat. u. Nervenkrankh.*, 1928, 84, 363) presents 9 cases of tetany with psychic manifestations, which were treated by meat-free diet including  $\frac{1}{4}$  to  $\frac{1}{2}$  liter of milk and 30 to 40 tablets of hemokrinin per day. In all of the cases the symptoms of tetany were found to be

correctable by this treatment. The psychic changes which he found to belong properly to the tetany syndrome were very closely related to the epileptic form of mental changes. He concludes that the tetanic attacks have a motor component of the extrapyramidal type and that the extrapyramidal system has an affinity for the parathyroid disturbances.

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## PATHOLOGY AND BACTERIOLOGY

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**The Pathology of Hemangioma of Bone.**—BUCY (*Am. J. Path.*, 1929, 5, 381) reports 7 cases while previously Toepfer claimed that the condition was present in about 12 per cent of autopsies. The lesions consist of a hard mass within the medulla which at times may show a soft and even pulsating center. They bleed profusely. The mass consists of large cavernous spaces filled with blood, and supported by bony trabeculae which show both degenerative and formative changes. Occasionally the endothelial character of the structure is suggested by the abundance of the foam cells. The author is uncertain whether these lesions are neoplasms or vascular malformations.

**Spontaneous Rupture of the Aorta.**—LIFVENDAHL (*Arch. Path.*, 1929, 8, 200) reviews the literature upon spontaneous rupture of the aorta, a term restricted to the condition of loss in the continuity of the vessel wall occurring without evidence of extrinsic pathologic changes, trauma, or formation of an aneurysm with secondary mural perforation. The author reports 3 cases of the condition, which came to autopsy in patients of middle age who suffered from hypertension, cardiac hypertrophy and from varying degrees of renal involvement. The Wassermann reaction of the blood was negative in the first 2 instances and not examined in the third. In the first case a triangular-shaped tear, 3 cm. above the valve involving the entire circumference of the aortic wall resulted in an effusion of blood which stripped up the intima and perforated the adventitia to fill the pericardial sac. In the second instance, the aorta evidenced only a few fatty plaques on its smooth intimal surface, yet presented a transverse slit in the intima and media two finger breadths above the aortic ring. An opening of pinhead size in the outer aortic wall permitted the extravasation of blood into the pericardium. The third case presented three tears in the aortic wall; the first opening into the pericardium, the other two being situated in the abdominal aorta. In each of the 3 cases reported, histologic examination of the aortic wall at the site of the lesion revealed typically

syphilitic changes. Spontaneous rupture of the aorta most frequently occurs at the points of relative fixation, one and a half finger breadths above the aortic cusps or in the region of the ductus Botalli. The author wishes to emphasize the fact that while gross changes at the site of a rupture are frequently inadequate to explain the tears, localized microscopic alterations of a syphilitic or degenerative nature may be marked.

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## HYGIENE AND PUBLIC HEALTH

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**The Oral Administration of Derivatives of Chaulmoogra Oil in Leprosy.**—WAYSON and BADGER (*U. S. Pub. Health Rep.*, 1928, 43, 2883) are cautious in expressing any opinion on the value of chaulmoogra oil preparations in leprosy, but point out disadvantages of the drug and its derivatives as ordinarily given. The writers employ an emulsion of the esters derived from the oil prepared by the use of acacia and syrup and cod-liver oil. The dose varies from 1 to 10 cc. per day, and the preparation usually is well tolerated.

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**The Thyroid Gland and Communicable Diseases.**—A study of the effects of communicable disease upon the size of the thyroid glands of elementary school children made by OLESEN (*U. S. Pub. Health Rep.*, 1928, 43, 3009) revealed the following: (1) Thyroid examinations of 589 boys and 636 girls were made before and after communicable illnesses. After the illness no changes in thyroid size were detectable among 51.7 per cent of the boys and 45.6 per cent of the girls. Thyroid size was decreased in 13.8 per cent of the boys and 11 per cent of the girls. Increased size was noted among 34.5 per cent of the boys and 43.4 per cent of the girls. (2) The thyroids of 1842 boys and 1783 girls who did not have communicable illness in the interval were examined one year apart. No change in thyroid size had taken place among 48.4 per cent of the boys and 43.6 per cent of the girls. Thyroid size had decreased in 12.7 per cent of the boys and 18.6 per cent of the girls, while an increase was recorded among 38.8 per cent of the boys and 35.7 per cent of the girls. (3) A communicable disease census of 7977 boys and 8441 girls showed little difference in percentage incidence among the thyroid-normal and thyroid-enlarged children who had the same maladies. The author concludes from his findings that there is some evidence to show that one of the immediate effects of communica-

ble diseases among girls of elementary school age is simple enlargement of the thyroid gland. However, this thyroid enlargement appears to be temporary in character. A comparatively short time, the length of which is as yet undetermined, after a child recovers from a communicable disease, he is no more prone to changes in thyroid size than a child who has not had a communicable disease. In so far as elementary school children are concerned, there appears to be no ground for assuming that the ordinary communicable diseases are responsible for simple goiter. The underlying causes of this malady must be sought for in other directions.

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## PHYSIOLOGY

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PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 21, 1929

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**Some Remarks on the Chemistry of Cell Division.**—FREDERICK S. HAMMETT (from the Research Institute of the Lankenau Hospital, Philadelphia). Cell division is an expression of reactions between chemical molecules. From this point of view the process is obviously self limited. The problem of the chemistry of cell proliferation therefore resolves itself into an inquiry as to the nature of the key group initiative of cell multiplication and which by its reaction products is inhibitive thereof.

Pb-ion was used as the reagent. It was found that the metal retards development of parts where growth by increase in cell number is most active in chick embryos<sup>1</sup> and root tips of seedlings of beans and corn.<sup>2</sup> The seedlings showed that this is due to inhibition of mitosis and not of growth by increase in cell size.<sup>3</sup> Chemical studies under the microscope brought out that a Pb compound is deposited in the region of active cell proliferation,<sup>4</sup> and that it is concentrated in the nucleus<sup>5</sup> particularly in association with cells undergoing division.<sup>6</sup> Chemical analysis of the deposit under the microscope and in the test tube showed it to be a combination of the metal with sulfhydryl.<sup>7</sup> Further it was found that -SH is concentrated in regions of active growth by cell multiplication. The hypothesis followed that sulfhydryl is specifically essential for growth of this type and that this is stopped by Pb because of removal of the activating group.

This hypothesis was tested by observing cell proliferation and cell size reaction in root tips and paramecium to thio-glycollic acid, di-thio-di-glycollic acid, cysteine, cystin, glutathione, ergothioneine, and insulin. As controls the equivalent compounds minus the -SH group were used when known. Experiments with thio-glucose on wound healing in rat and man were also done.<sup>8</sup> In all cases where labile -SH was present, acceleration of cell proliferation obtained, and no stimulation of cell growth in size. The work as a whole, then, establishes the fact the the sulfhydryl group is specific and essential to cell growth in

number.<sup>9</sup> Details as to methods of procedure are to be found in the papers cited.

If the premises stated at the beginning be correct, it should be expected that, according to the law of mass action, the products of reaction of the effective group would be inhibitive of cell proliferation. Recent experiments with oxidized products of thio-glycollic acid, thio-glucose, and other simple sulfhydryl derivatives show this to be so. The data so far, then, justify the conclusion that cell division is regulated by a chemical equilibrium in which  $-SH$  is the key group.

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**Gastric Motility Studies—Ruminant Stomach.**—R. S. AMIDON (from the School of Veterinary Medicine, University of Pennsylvania). The physiology of digestion as it occurs within the ruminant stomach has received but a limited amount of experimental study. Such data as are available today represent the investigational effort of but a limited number of workers whose studies have been conducted three to eight decades ago. The contributions of Colin, Flourens, Chauveau, Tous-saint and Ellenberger are among the most important and have to serve to clarify many of the problems encountered in this interesting field of physiology, especially as regards the mechanics of the digestion process.

In 1921 the author, collaborating with Dr. A. F. Schalk of the North Dakota State College, undertook a study of the motility factors for the purpose of reviewing and enlarging if possible upon the existant experimental data pertaining to this subject. The ox was selected as the experimental subject. A gastric fistula 4 to 6 inches in diameter was established in the left flank region of each animal, this opening communicating with the first and second divisions of the compound stomach. These large fistulæ did not disturb the normal body functions in any appreciable manner some of the animals being kept under observation for a period of two years. It was of course quite essential that the fistulæ be closed whenever observations were not in progress. This was accomplished by a special valve-like device constructed of wood and leather which served to guard against any serious loss of gastric contents and the effects of cooling and drying of the gastric mucosa. Observations were secured by means of graphic records, palpation and visual inspection. The third (omasum) and fourth (abomasum) divisions of the stomach were not freely accessible to study and the data secured relate chiefly to the functional activity of the first (rumen) and the second (reticulum) portions of the organ.

The most important results obtained from this study are as follows:

1. Details were secured concerning the frequency, sequence, etc., of the contractions in the four divisions of the stomach.



2. The source of the material forming the bolus of rumination was definitely proved to be from the reticular cavity.

3. The esophageal groove is nonfunctional in mature animals but is active and serves to guide milk into the abomasum of the nursing calf.

4. Pressure and friction stimuli when applied to the gastric mucosa per fistula will initiate the act of rumination. Such stimulation is probably representative of the effects exercised by the heavy coarse food material taken into the rumen and reticulum.

5. No digestive secretions are elaborated in first three divisions of the ruminant stomach. Fermentation, which occurs in a very active manner within the rumen and reticulum, releases valuable nutritive materials from their cellulose investments so that the digestive secretions of the abomasum and intestinal region are enabled to accomplish their action.

6. The importance of abundant moisture within the stomach has been especially emphasized in this work and has a practical significance in the treatment of rumen impaction.

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**The Effect of Posture on the Cardiac Output.**—ISAAC STARR, JR., and LEON H. COLLINS, JR. (from the Laboratory of Pharmacology of the University of Pennsylvania). Two series of experiments have been completed to extend the use of the improved ethyl iodid cardiac output method (STARR and GAMBLE, 1928) to normal subjects standing at rest. These experiments demonstrate that:

1. In the standing position the ethyl iodid content of arterial blood may be estimated from the content of alveolar air collected automatically (five experiments).

2. If a standing subject, after inhaling ethyl iodid, rebreathes for thirty seconds in one bronze bag, then for a minute longer in a second bag, the agreement between the ethyl iodid content of the two bags is not as close as in the supine position; that of the second bag averaging 13.6 per cent below that of the first. Therefore the equilibrium between the ethyl iodid in mixed venous blood and that in air rebreathed for thirty seconds cannot be so closely demonstrated as in the supine position. However any error in estimating ethyl iodid in mixed venous blood must be small and in the direction of making the calculated blood-flow smaller than the actual in the standing position.

Ten duplicate determinations of cardiac output in both the standing and supine positions have been made on five subjects. In four subjects no significant change of cardiac output followed the change from supine to standing position or the reverse (seven experiments). These results are similar to those of Grollman. In one subject the bloodflow standing was always significantly less than that lying (three experiments). This subject had a history of occasional fainting without obvious cause, the others had no such history.

If the results are calculated from our data according to the method of Henderson and Haggard the cardiac output always appears much smaller in the standing than in the lying position. The addition to this calculation of the factor representing the ethyl iodid content of venous blood brings the result in both positions to the same figure in four of our five subjects.

**A Comparison of the Histology and Physiology of the Sensory End Organs of the Prepuce.**—R. G. WILLIAMS, B. MCGLONE and H. C. BAZETT (from the Department of Physiology, University of Pennsylvania). *Histological.* When pieces of skin are stained with methylene blue and cleared in oil of wintergreen it is possible to observe large numbers of nerve endings and to determine their depths and relations without recourse to sections and reconstructions.

The following data were obtained from skin removed at circumcision which had been treated in such a manner. The data presented represent a study of one square centimeter of skin. Studies on other square centimeters show no appreciable variation from the one given.

One square centimeter of skin contained 212 nerve endings which were quite evenly distributed. Of this number there were seven types: 115 were free endings which occurred at a depth of 56 to 72 micra; 52 were very small end bulbs having a very fine net arrangement but no capsule and occurring at a depth of 20 to 28 micra; 23 were free endings having a brushlike arrangement at the end of numerous branches and being at a depth of 40 to 60 micra; 15 were the so-called Krause endings which occurred at a depth of 64 to 72 micra; 4 were an unusual type having a thick, pale capsule and a central nerve core which occurred at a depth of 92 to 140 micra; 1 corresponded to Ruffini's ending at a depth of 200 micra; and one was a Meissner ending which lay at a depth of 140 micra.

The normal thickness of the skin in this region being 0.6 mm. the shrinkage of this specimen was 30 per cent. When the figures are corrected for shrinkage the depths of the end organs would appear to be as follows:

Type I . . . . .	80-103 micra
Type II . . . . .	28.6-40.0 micra
Type III . . . . .	57.1-85.5 micra
Type IV (Krause) . . . . .	91.4-103 micra
Type V . . . . .	131-200 micra
Type VI (Ruffini) . . . . .	285.7 micra
Type VII (Meissner) . . . . .	200 micra

A determination of the depths of the bloodvessels of the prepuce from a completely injected and cleared specimen indicates that in general the Ruffini end organs lie in the deep rete venosum of Spalteholz, those of Meissner lie in the superficial rete venosum, and the Krause endings lie in the arteriovenous region immediately below the corpus papillae of the corium.

*Physiological.* A fold of tissue covered on both sides with skin is obtained by suspending a part of the prepuce or a fold of loose skin from the dorsal surface of the penis by two hooks connected to weights (30 gms.) over pulleys. The sensitive spots are mapped. It is found possible to stimulate the end organs sensitive to temperature from either side, though the latency of sensation is less, when the stimulus is applied to the spot nearer to the end organ. The thickness of the fold is determined from Roentgen ray photographs, the time of thermal penetration by the use of thermocouples, and comparison with the latencies of sensation permits calculation of the probable depths of the end organs involved.

*Touch.* The threshold for touch has been a pressure of about 1.5 gm. per mm. radius, applied with a hair (von Frey's technic). The reaction time to touch sensations is in this area very variable; the minimum has been 0.11" to 0.14" (3 subjects); the median value has varied from 0.25" to 0.31".

One square centimeter of skin ruled in sq. mm. areas (rubber stamp) gives positive responses to touch stimuli (2 gm. per mm. radius) in 31 to 64 per cent of the squares tested.

*Cold.* The reaction times are variable—the minimum recorded was 0.23". The cold spots are distributed irregularly. When determined with a point of 1.5 mm. diameter their number varies between 2 and 11 per sq. cm. When mapped more carefully with a cooled wire of  $\frac{1}{8}$  mm. diameter the maximum number observed has been 12 per sq. cm. Calculation of depth from variations in reaction time indicates a value of 0.1 mm. as the most probable.

*Warm.* The reaction times are less variable than those of cold, the minimum recorded was 0.40". The warm spots are usually related to visible veins. Their number varies between 0.5 to 2 per sq. cm., with a median value of 1 per sq. cm. The calculated depth is most commonly 0.35 mm.; occasionally depths of about 0.5 mm. are estimated. The total thickness of a double fold has usually been 1.2 mm.

Both with warm and cold there is no doubt that stimulation can be induced from either surface, even though thermal gradients must be quite different. At the depths estimated for the end organs vascular plexuses probably exist; it has appeared easier to stimulate cold and warm end organs by lateral transmission of thermal changes when the application is made distally as estimated by the direction of the veins. Conduction along the blood stream is probably an important factor.

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